The Hereditary Transmission of Defects in Man

Dissertation for Degree of Doctor of Medicine
in the University of Oxford

BY

EDWARD STAINER

M.A., M.B., B.Ch. Oxon.

OF ST. THOMAS'S HOSPITAL, LONDON

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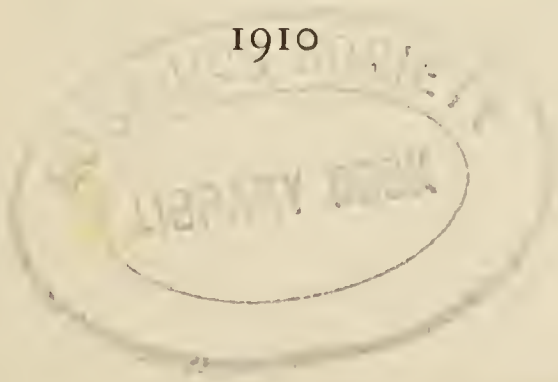

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THE HEREDITARY TRANSMISSION OF DEFECTS IN MAN

INTRODUCTION

The story of the inheritance of defects is one which seems to speak of little failures here and there in the evolution of perfect man.

Civilization may cherish with care all that is good and strive to stamp out all that is bad of the inherited qualities of man, but nevertheless she takes pity on many of her defective children and allows them to hold their own in the struggle of life.

Defects of various kinds and degrees have arisen, and no doubt do continue to arise spontaneously in families, to be handed down from generation to generation often with extraordinary persistence. If the presence of these defects indicates that all is not as it should be in the progress of man, the blame must undoubtedly be laid on marriages which are contracted with such tainted families. The mating of man and woman is determined by a variety of circumstances, and the question of the influence of heredity on the generation to come is only one of many which have to be considered.

Happy optimism rules the world when marriage is contemplated, and inherited defects are therefore often left to take care of themselves.

Inheritance, nevertheless, is the power which determines the future welfare of the race, in that it exerts its

subtle influence not only for the perpetuation of good qualities, but for the persistence in families of all characters, good, bad, and indifferent. Good qualities, from their very nature, tend to assert themselves for the benefit of the individual and the race, but bad and indifferent characters have their chance too, when inheritance is allowed to act with a free hand.

What this chance amounts to as far as the family is concerned, we will now attempt to estimate by considering the hereditary transmission of defects in its various aspects.

Key.

Defective.

♂ male ♀ female ● Sex unknown

Normal.

♂ male ♀ female. ○ sex unknown

(4) The figure indicates the number of normal children.

←●→
←○→ The arrows indicate that there are other brothers and sisters.

a 'childship' is the family of children resulting from a marriage.

THE TRANSMISSION OF DEFECTS

PEDIGREES dealing with the hereditary transmission of defects demonstrate clearly that there is much variety in the way in which these defects are handed down in families.

For general purposes transmission may be considered as of two kinds, direct and indirect.

Direct transmission may be said to occur when the defect is present in both a parent and a child, so that the defect comes directly from the parent to the child.

Indirect transmission occurs when a child has a defect which is absent in both parents, so that the defect comes to the child through one of the parents.

It may be possible by the discovery of other defective members in the family to decide which parent is responsible for the indirect transmission, but often there is an entire lack of evidence on this point.

In some cases this want of evidence may be due to the limited size of the family, but in other cases it means that relations have drifted apart, with the result that little or no information can be obtained on family matters.

In the absence of any history of a defect occurring in either the paternal or maternal families, there is, it is true, a possibility that the defect has arisen in the childship spontaneously, in which case we are merely observing the first appearance of the defect in the family.

Whilst admitting this possibility, we will assume for our present purpose that when a childship is tainted with a defect, this same defect has, in the majority of cases, already existed in some previous generation of the family.

The contrast between direct and indirect transmission, then, depends on the presence or absence of a defect in the parents. If a parent has a defect, he or she may be termed an abnormal, and as a transmitter of the defect to the childship may be called a bearer of the defect.

If a parent displays no defect and yet transmits a defect to the childship, he or she may be called a carrier of the defect.

It is the relative proportion of these bearers and carriers in tainted families which causes so much variety in what may be termed the transmission-pedigrees of hereditary defects. In one family, for instance, every abnormal may be seen to have inherited the defect directly from one of the parents, whereas in another family the defect is always transmitted indirectly. In other families, again, we find the transmission-pedigree complicated by the fact that both bearers and carriers exist side by side, so that the defect is perpetuated by both direct and indirect transmission.

Then, in addition to these possibilities, we find the two sexes showing certain peculiarities when acting as bearers or carriers. In one family the males may be conspicuous by the way in which they transmit directly only to their male children, and in another family the females may with remarkable uniformity play the part of carriers transmitting indirectly only to their male children. Then, again, we may come across a family in which the females alone appear to be defective, whilst the males tend to act only as carriers.

In fact, there is so much variety in the way in which defects can be transmitted in families, that at first sight a search for evidence of law and order would appear to be a hopeless undertaking. If, however, we turn to individual families, we begin to realize that the trans-

mission cannot be a mere matter of chance, for we frequently find that the peculiarities of transmission obvious in one generation tend to be repeated in the next generation. For this reason it is possible to recognize certain types of transmission which have their own

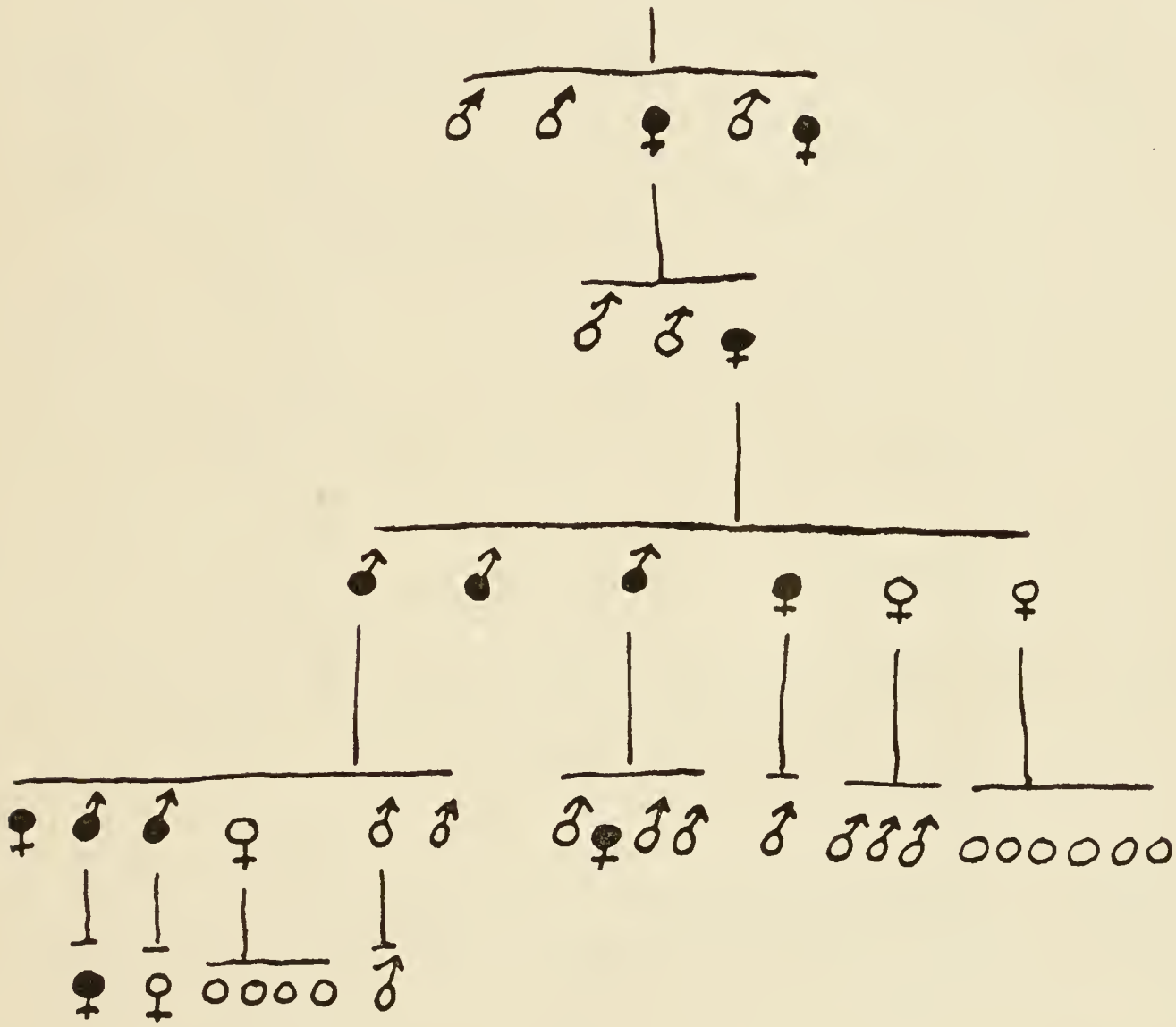


FIG. 1. COLOBOMA IRIDIS.
Simeon Snell, *Trans. Ophth. Soc. U.K.*, vol. xxviii, 1908, p. 148.

distinctive characters. The first type to be considered may be called common direct transmission, which has the following characters :—

1. The transmission is always direct from the father or mother to the childship, so that only bearers are to be found in the transmission-pedigree.

2. In a tainted childship the males and females are

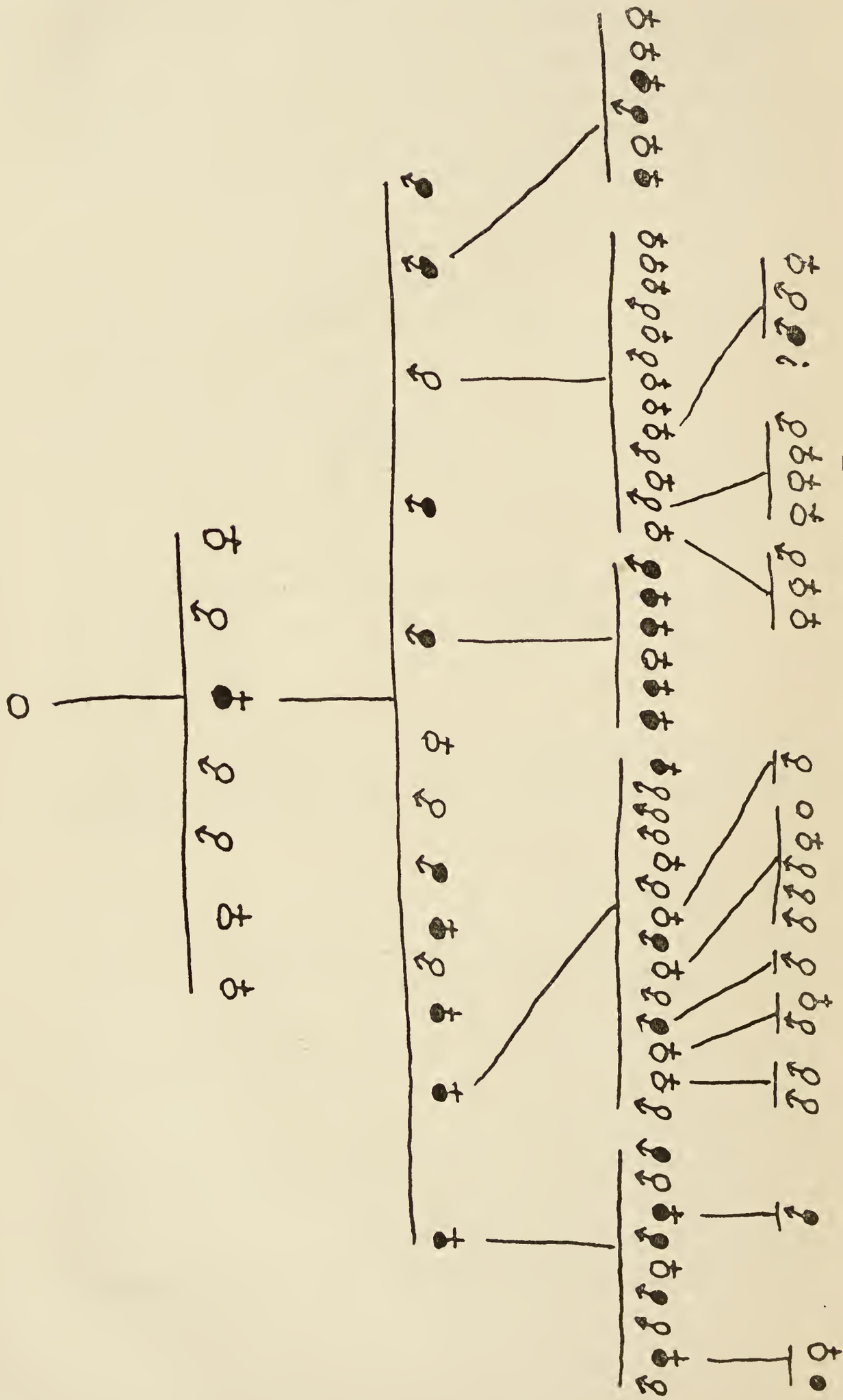


FIG. 2. INHERITED CONGENITAL CLAW FOOT.

H. B. Robinson and W. H. Bowen, *Proc. Roy. Soc. Med.*, May 1909, p. 206.

about equally liable to the defect, and for each sex there are as many normals as there are abnormals.

Many pedigrees dealing with different structural defects could be brought forward to illustrate this type of trans-

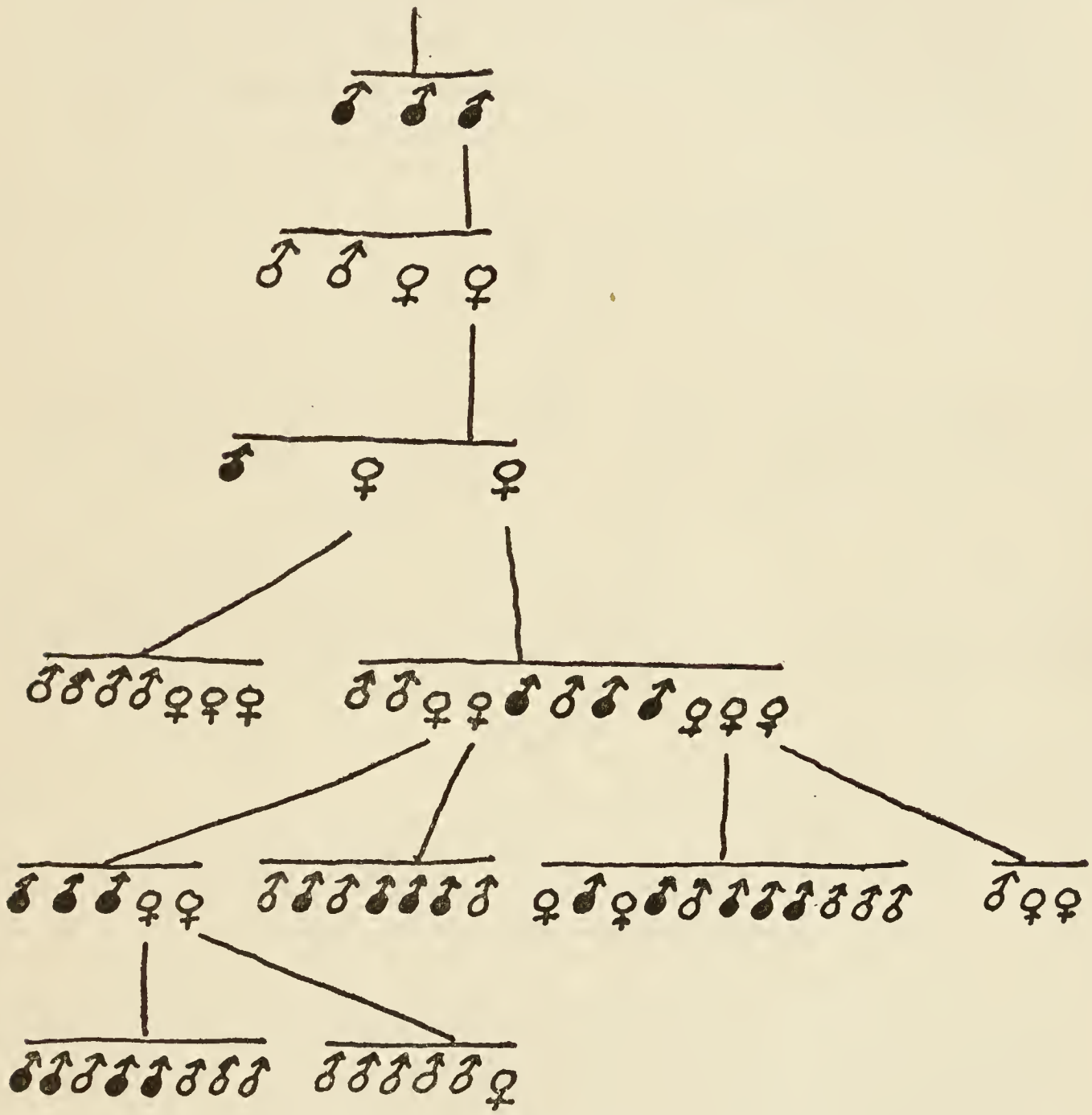


FIG. 3. HAEMOPHILIA.
Wickham Legg, *Bart.'s Hosp. Reports*, 1881.

mission, but here we propose to consider only two families which are thoroughly representative of the type.

In the first family (Fig. 1) a partial or even total absence of the iris is the inherited defect, and in the second family (Fig. 2) there exists a striking malformation

due to the absence of a varying number of the small bones of the hands and feet.

It will be seen that the males and females are defective in about equal numbers, and that they as bearers pass on the defect to about one half of their children.

These and many similar pedigrees teach us that common direct transmission is a very important factor in inheri-

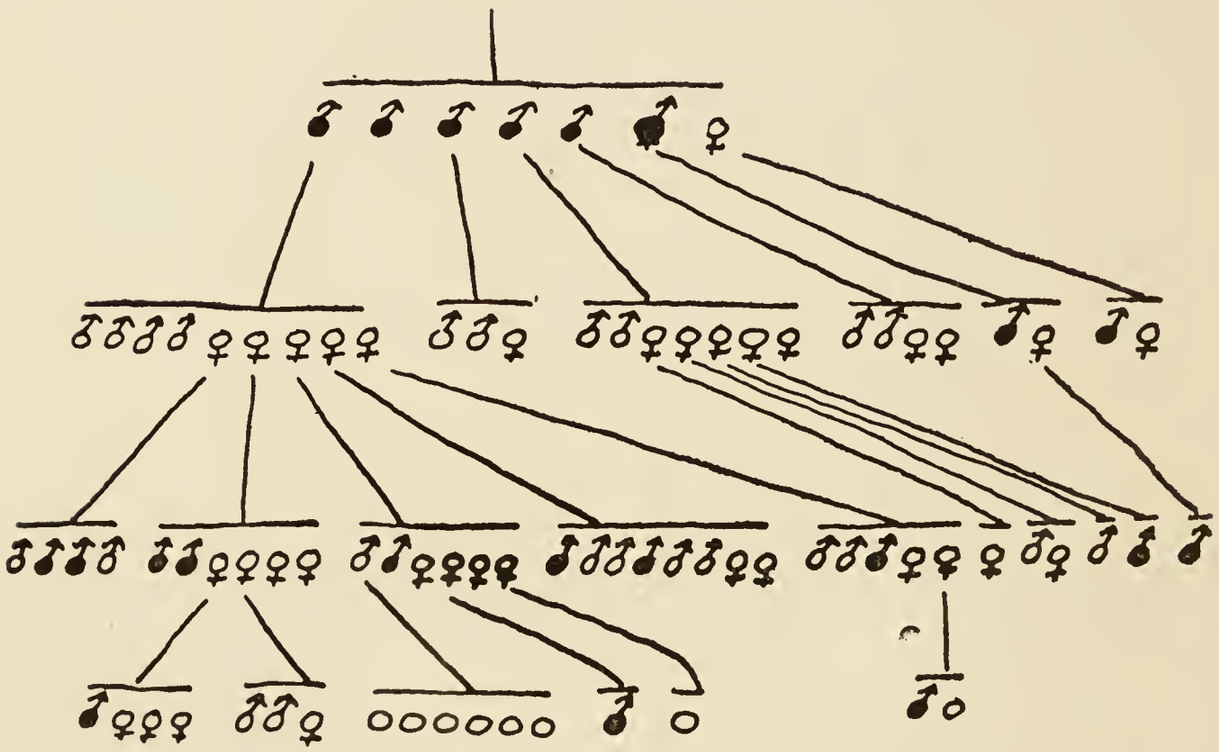


FIG. 4. MUSCULAR ATROPHY OF THE PERONEAL TYPE.
W. P. Herringham, *Brain*, vol. ii, p. 230, 1888.
A. E. Russell, March 1905 (Private Notes).

tance, and we are probably justified in considering it as an expression of the first principle of inheritance, that like tends to produce like.

If defects were always transmitted in this simple manner transmission-pedigrees would show a monotonous similarity, but this is far from being the case.

Another striking type of transmission proves conclusively that common direct transmission is by no means essential, and that indirect transmission can play an important part

in inheritance. In this type the transmission goes indirectly through the females and the males only are affected.

It may be called the carrier female type of transmission, and it is well known owing to the fact that it is the prevailing type by which Haemophilia is handed down in families, although it is by no means peculiar to Haemophilia, as the following pedigrees will show.

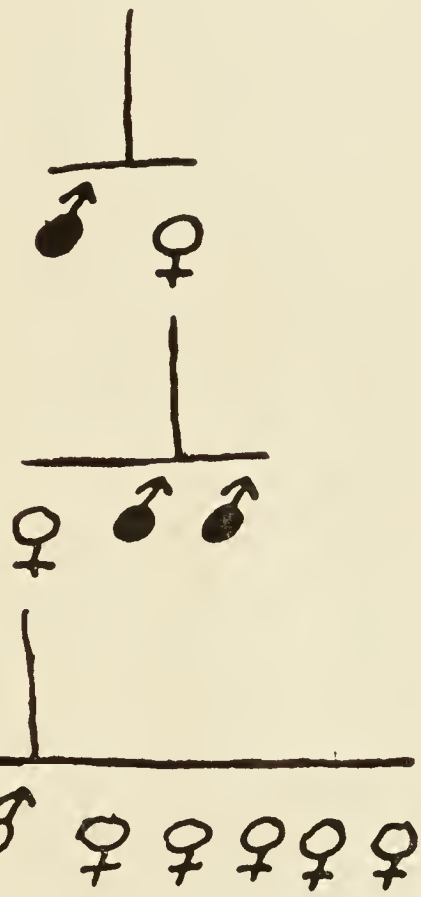


FIG. 5. PSEUDO-HYPERTROPHIC MUSCULAR PARALYSIS.
Russell, *Med. Times and Gaz.*, May 29, 1869.

The first pedigree (Fig. 3) shows how Haemophilia in its severe form may kill off large numbers of males in a family.

There are twenty-three haemophilic males in the pedigree, and of these eighteen were known to have died of haemorrhage from various causes. The frequency of deaths at an early age speaks of the serious gravity of the defect.

One baby 2 days old died of haemorrhage as a result of a blood-tumour on the scalp being opened, and another boy, 2 years old, died of bleeding from the mouth.

A bitten tongue caused the death of a 3-year-old, and two other boys of the same age died of haemorrhage from the mouth.

Two boys died at the age of 4, one from nose-bleeding and the other of haemorrhage from a wounded finger.

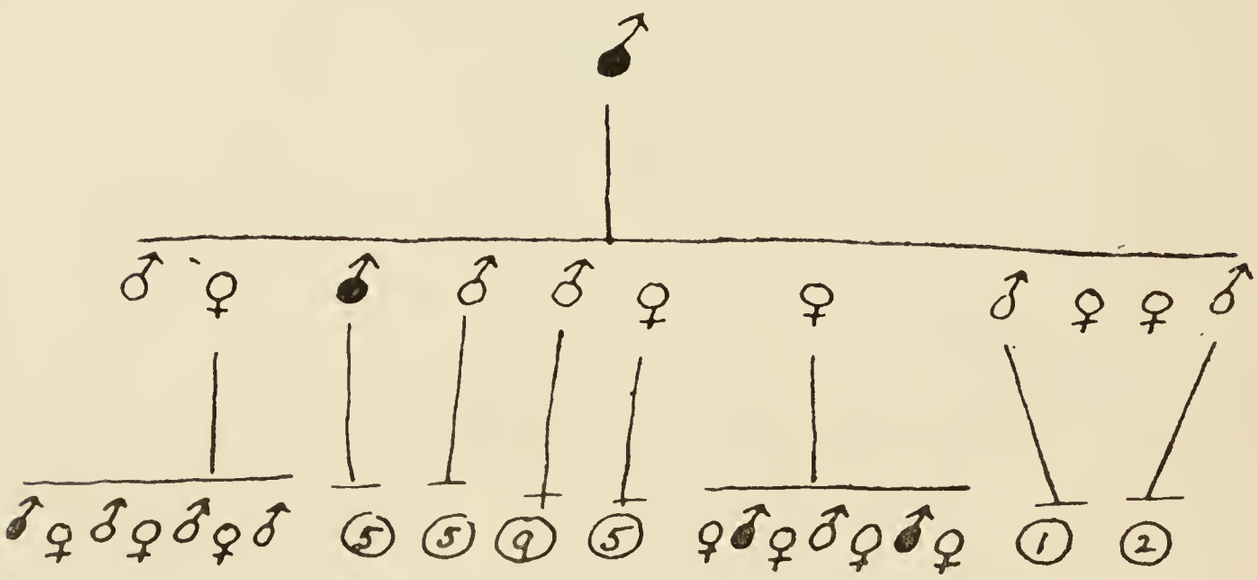


FIG. 6. HEREDITARY OPTIC ATROPHY.
Rayner Batten, *Trans. Ophth. Soc. U.K.*, vol. xxix, 1909, p. 144.

To complete the list, four boys died at 7 years old, and of these the haemorrhage came from the mouth in two cases and from the bowel in another case, while an accidental wound on the head caused the fatal bleeding in the fourth case.

The second pedigree (Fig. 4) deals with the transmission of a progressive muscular atrophy which started in the legs usually before puberty.

Although the wasting tended to cripple, it did not cause the early death so noticeable in the third family (Fig. 5). Here, with another variety of muscular atrophy,

we have an early onset of the disease with death following a few years afterwards. In the case of the two boys of the second generation, the onset was at the age of 9 in each case, with death at the ages of 16 and 17.

Of the three brothers in the last generation, the first started the atrophy at 4 years old and died at 16, the

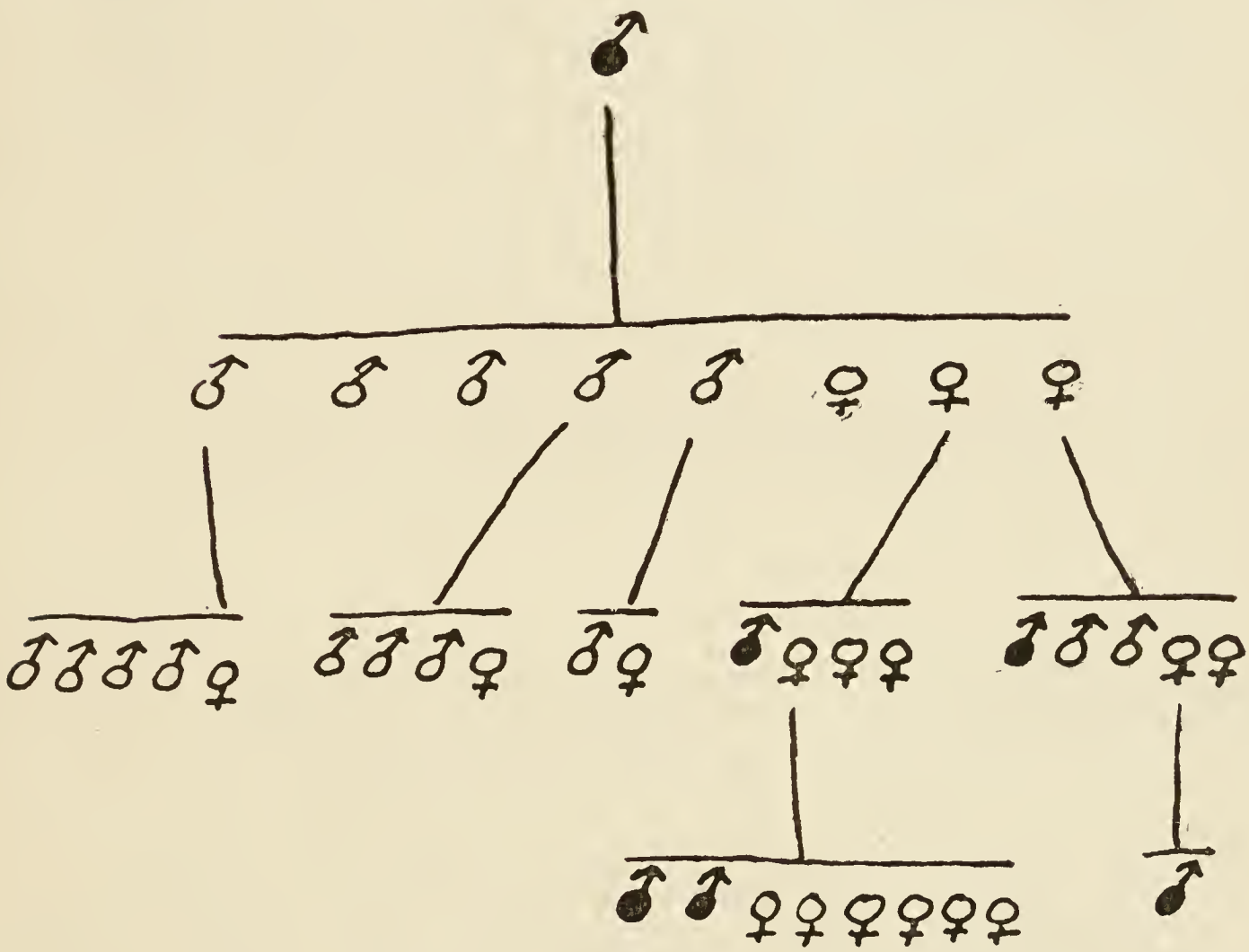


FIG. 7. COLOUR BLINDNESS.
Fontenay's Case, *Archives of Ophthalmology*, vol. x, 1881, p. 8.

second had the onset at 9 and died at 13, whilst the third with the onset at 3 was still alive when 10 years old.

The fourth pedigree (Fig. 6) deals with failure of sight as an hereditary defect, and in the last generation there are three abnormal males. The first had failure of sight at the age of 20, and there was no improvement in the condition three years afterwards.

The second had gradually failing sight commencing at 16, and his younger brother, the third case, had rapid failure of sight at the age of 10, with marked improvement of sight later.

The fifth pedigree (Fig. 7) shows the form of transmission usually associated with the well-known defect of colour-blindness.

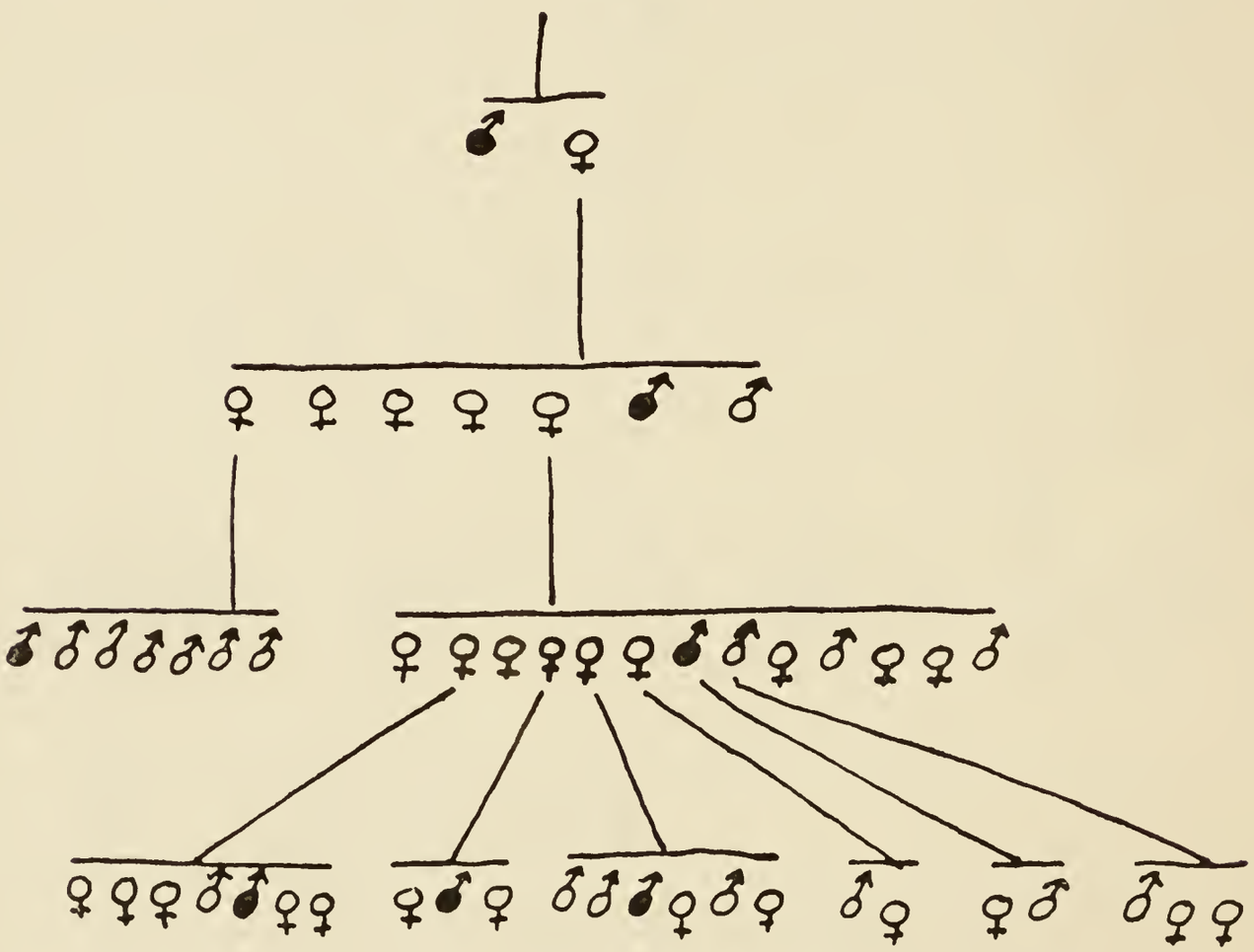


Fig. 8. Ichthyosis.
H.B., October 1897, St. Thomas's Hospital.

The sixth (Fig. 8) deals with a skin disease in which the skin is dry, rough, and dirty, and very liable to be irritated by external agencies.

It is not a disease dangerous to life, but in its more severe forms the life of the patient is more or less a miserable one.

The seventh of the series (Fig. 9) is interesting in that it deals with a defect of the hands which was apparently insignificant.

In addition to these families, Mr. Nettleship shows in his Bowman Lecture (1909) that the same type of transmission can be found in families tainted with Retinitis Pigmentosa and Hereditary Night Blindness.

Thus in nine widely differing defects we have striking evidence of the importance of the carrier female type of

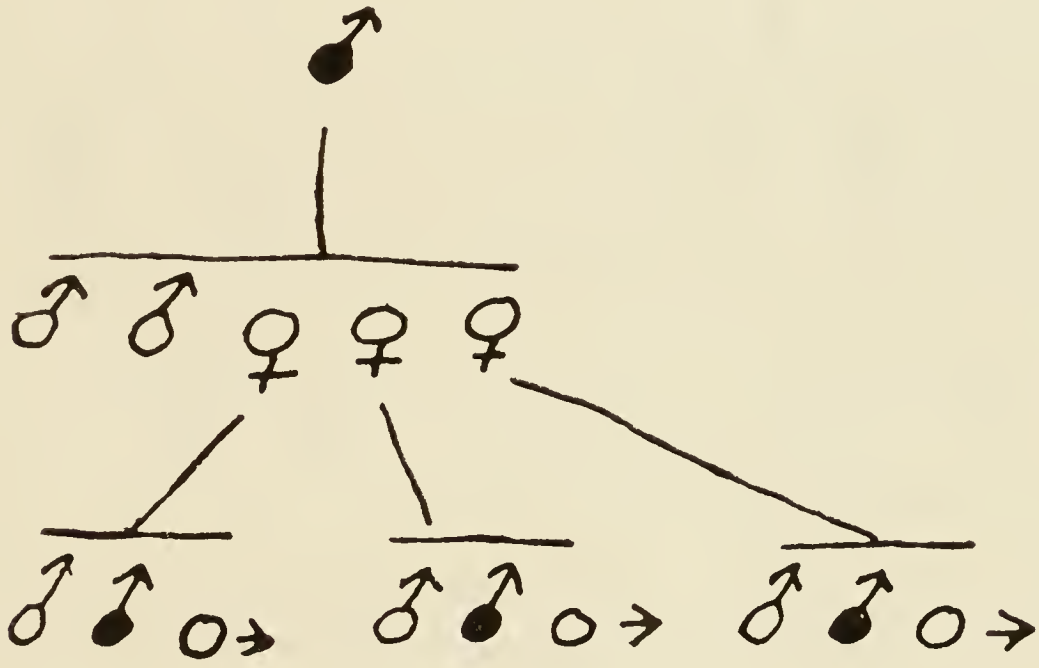
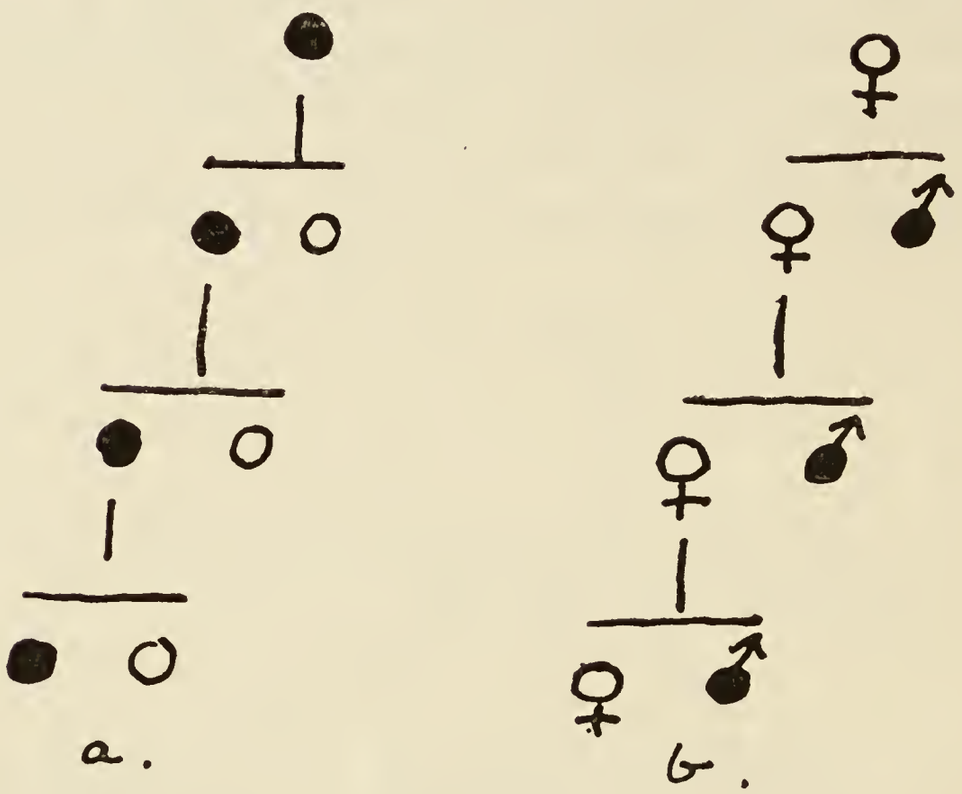


FIG. 9. CONGENITAL MALFORMATION OF LITTLE FINGERS.
Dr. J. Payne, *The Relation of Cancer to Life Assurance*, 1897.

transmission, and since the persistence of the defect is almost entirely dependent on the marriages of perfectly normal females, there seems no reason why the defect should ever be lost to the family.[1]

[1] This type of transmission has been called the 'Knight's move', but this is an unsuitable and somewhat misleading term. It must be borne in mind that the transmission comes through the mother, and that an abnormal uncle is in no way responsible for the defect appearing in his nephew. All the responsibility, as far as heredity is concerned, rests entirely on the mother.

The carrier type of transmission may now be compared with common direct transmission by exhibiting the salient features of each in the following pedigree-formulae :—



a. Common direct transmission.
b. Carrier female transmission.

There is so much contrast between the two types that at first sight it seems impossible to believe that they could have come into existence under any uniform principle of inheritance. At the same time it is improbable that there are two distinct processes at work so that the one type stands in no kind of relation to the other type.

If common direct transmission is accepted as the simple expression of an hereditary process, there must be some influence at work for the production of the indirect type which is absent in the case of the direct type.

The influence of the more severe defects in checking marriage is certainly worthy of consideration in this respect.

Some of the hereditary defects, such as Haemophilia and Pseudo-hypertrophic Paralysis, when existing in a severe form cause death at an early age, so that marriage is an impossibility. Other defects, such as Leber's Optic Atrophy and Retinitis Pigmentosa, may produce a serious failure of sight at a comparatively early age, and so interfere with the prospects of marriage.

It is in these cases that we find the carrier female type of transmission most marked, and thus it is possible to formulate the rule that when a defect has reached a degree of severity so as to interfere with marriage, it will be found only in the males with the transmission only through the females.

Since direct transmission becomes of necessity an impossibility in many such families, the carrier female type, being the only type found under these conditions, must therefore be looked upon as the only type capable of surviving quite apart from any question as to its origin.

It is sufficiently clear that the actual severity of the defect cannot directly cause the carrier female type to appear in families, for pedigrees show that the type is equally persistent in families in which a defect does not in any way interfere with marriage.

The origin of this type of transmission in families therefore becomes an interesting subject for discussion.

The first possibility is that normal females have invariably transmitted the defect to their sons from the time that the defect first appeared in the family. This implies a spontaneous origin of one particular type of

transmission which would be exceedingly difficult, if not impossible, to prove by observation.

A more satisfactory explanation may, however, be offered, and this with the support of a considerable amount of evidence.

The more serious defects, such as Haemophilia and Pseudo-hypertrophic Paralysis, are, it is true, usually transmitted through normal females to males, but this is not always the case, for in families tainted with milder forms of these diseases affected females may be found in addition to the affected males. The type of transmission is in this way changed, so that it is possible in some families for the defect to be handed down by common direct transmission.

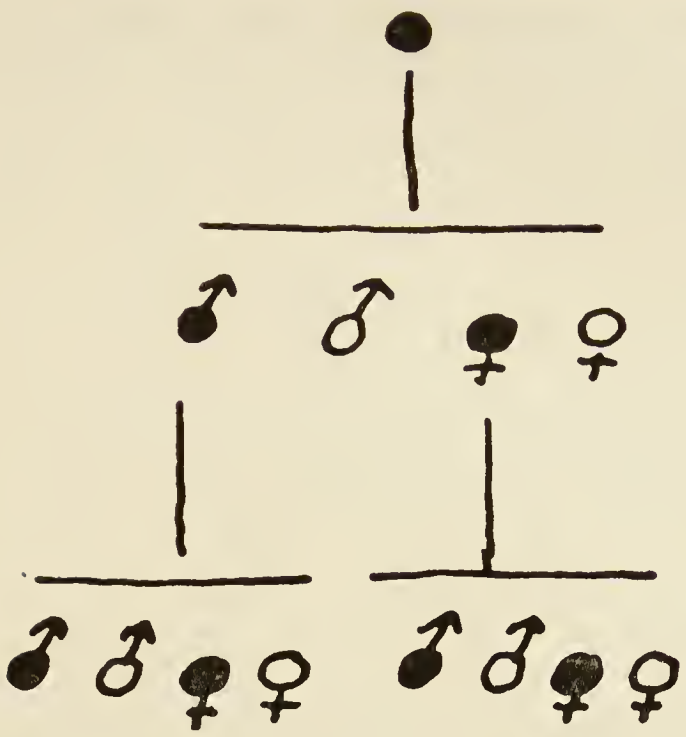
Now, if in these families showing common direct transmission the defect became more severe, we should expect the family to change its type of transmission to the type usually found with the severe form of the disease.

Here, then, is a possibility that the carrier female type of transmission does not owe its existence to spontaneous origin in a family, but rather to a gradual evolution from ordinary direct transmission.

If this gradual change does actually take place we should certainly expect to find in families all the intermediate steps in the change from one type to the other.

There seems to be little doubt that such an evolution does occur, and we will therefore attempt with the aid of transmission-pedigrees to show how it is brought about.

Starting with common direct transmission, our pedigrees may be considered to satisfy the following formula, in which there is an absence of carriers and an equal proportion of abnormal males and females.



This formula holds good as long as carriers are not found in the family, but as soon as they begin to appear the whole character of the transmission becomes changed.

The following pedigrees, for example, show how direct and indirect transmission can exist side by side in families.

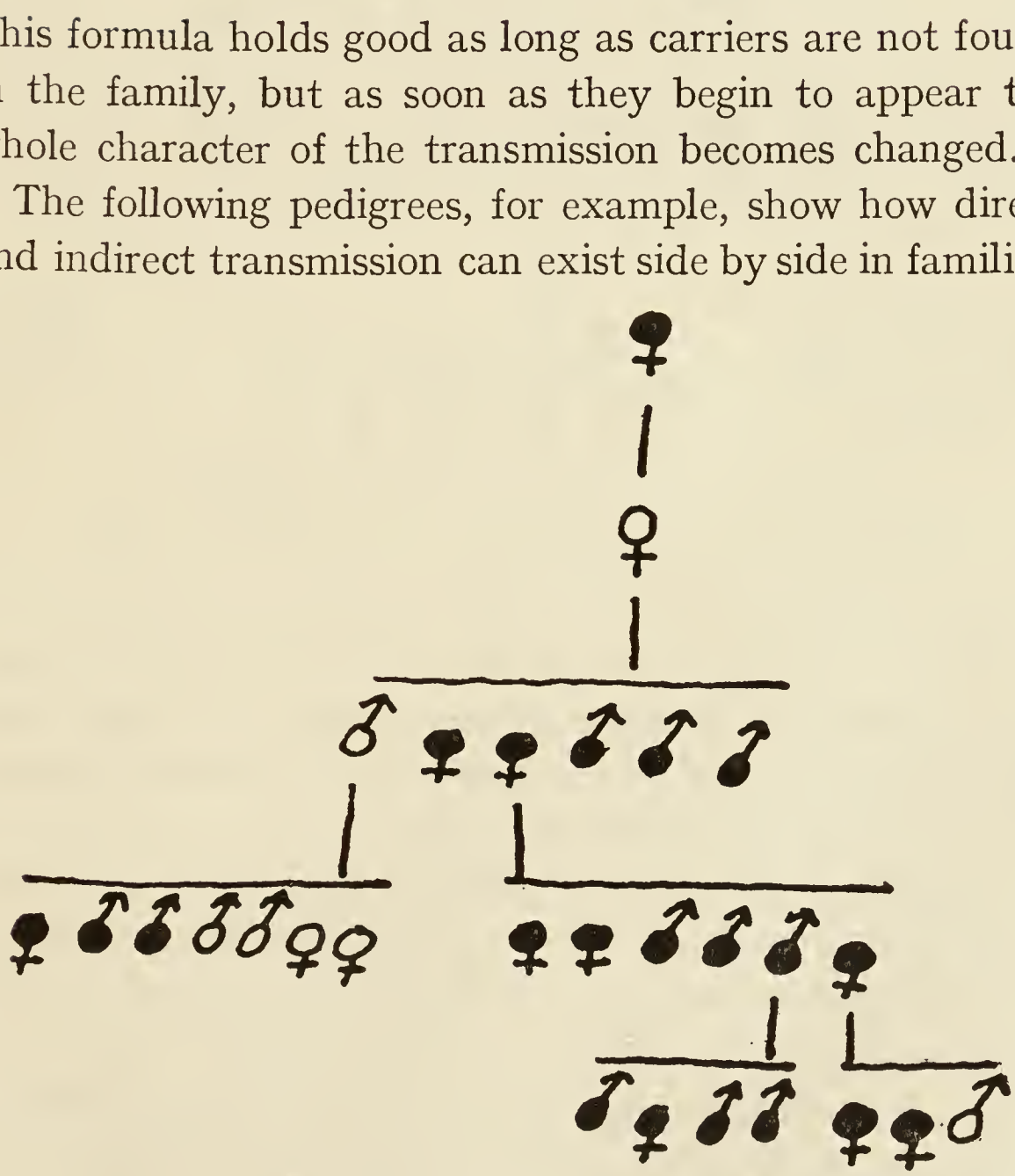


FIG. 10. MALFORMATION OF HANDS AND FEET.
Ramsay Smith, *Brit. Med. Journ.*, July 1894.

Here it will be noticed that both a male and a female are acting as carriers, and handing down a structural defect to the males and females of their respective childships.

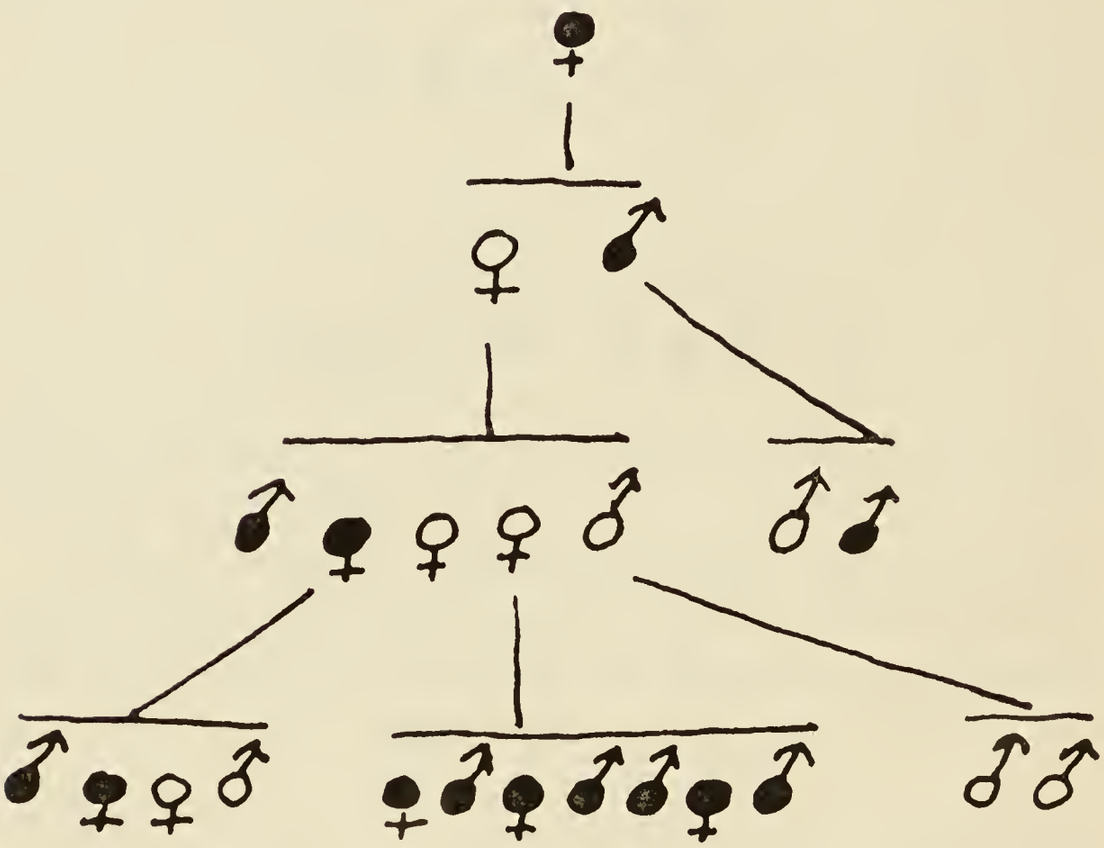


FIG. 11. HEREDITARY OPTIC ATROPHY.
Norris, *Trans. Amer. Ophth. Soc.*, 1880–4, p. 662.

We have already shown (Fig. 6) that this disease can be transmitted through females with the males only affected, but in this family there are six abnormal females in addition to nine abnormal males.

It is obvious from the pedigree that the disease was not severe enough to interfere with marriage, and this is interesting because in ten of the cases the onset of the atrophy was between the ages of 13 and 20.

The indirect transmission is due to the marriages of two female carriers, and it should be noted that the defect in

both cases was passed on to the daughters as well as to the sons.

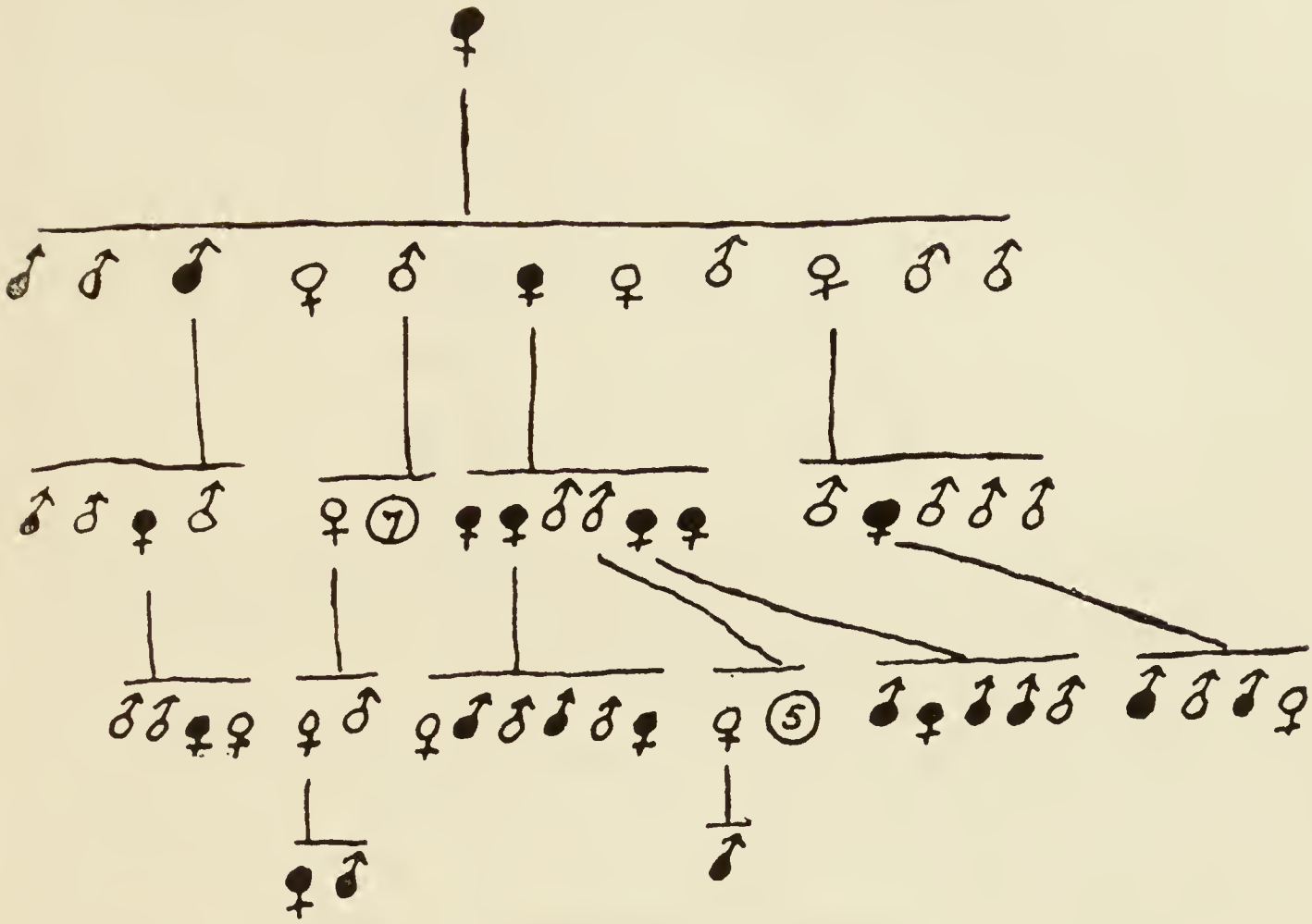
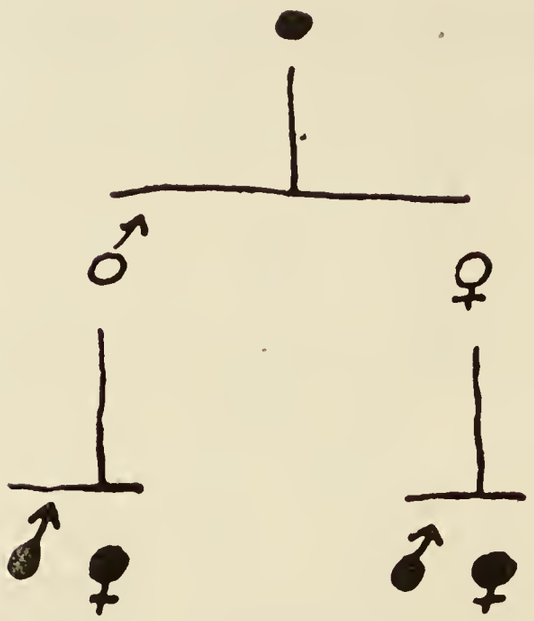


FIG. 12. HEREDITARY ATAXIA.
Sanger Brown, *Brain*, vol. xv, 1892, p. 250.

In this family (Fig. 12) the ages at which the first nervous symptoms appeared range from youth to middle age.

It will be noticed that both male and female carriers are taking part in the transmission, although most of the transmission is due to male and female bearers.

These three families teach us that indirect transmission may exist in some branches of a family while common direct transmission is evident in other branches of the same family. This indirect transmission may be roughly expressed by the following pedigree-formula



which serves to emphasize the fact that both males and females act as carriers, and that they both pass on the defect to their male and female children.

Since this type of indirect transmission is found closely associated with common direct transmission, we may conclude that it represents the actual origin and commencement of indirect transmission in a family.

Although we cannot pretend to understand why carriers should in this way appear in a family, it is clear that their presence causes considerable changes in the character of the transmission. In the first place, carrier females tend to outnumber carrier males, and this is a noticeable feature of all indirect transmission, even if we leave out of count all families which show only the carrier female type of transmission.

In the second place, indirect transmission leads to a definite reduction in the proportion of defective children in the childship.

This reduction is not so noticeable in families (Figs. 10, 11, 12) which probably show the origin of indirect transmission, but it becomes more apparent in families in which carriers take a more important part in the transmission.

For instance, an Ichthyosis family with direct transmission (Fig. 13) may be compared with another family in which indirect transmission is a feature (Fig. 14), and

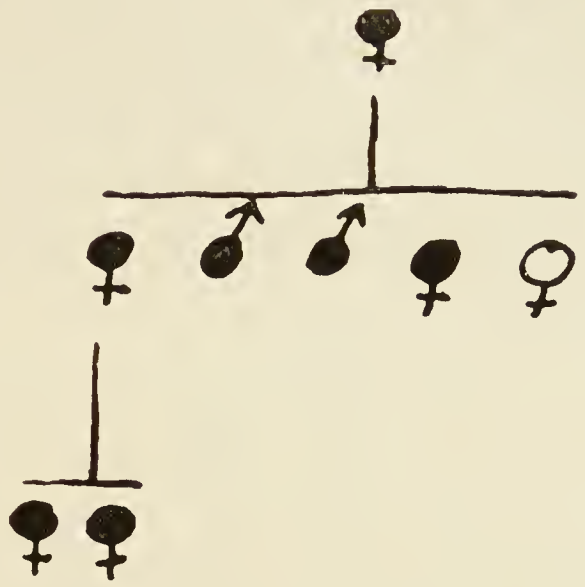


FIG. 13. ICHTHYOSIS.
A. W. P., St. Thomas's Hospital, 1900.

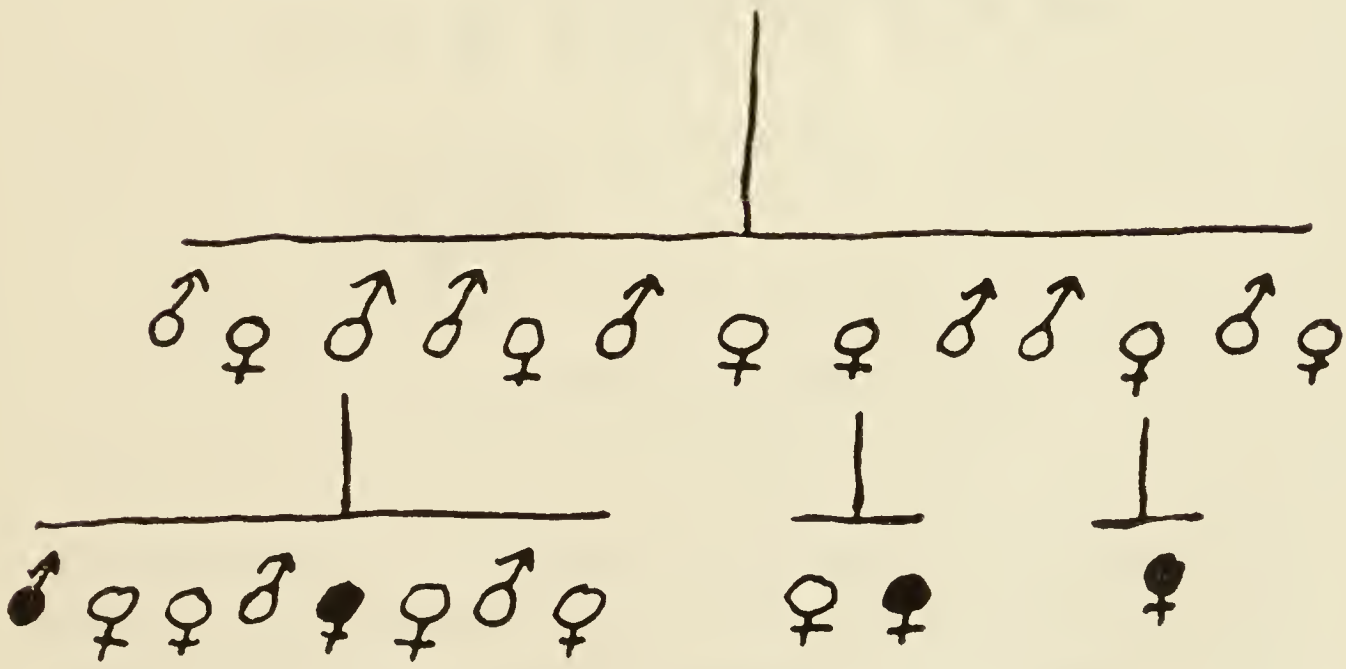


FIG. 14. ICHTHYOSIS.
W. W., St. Thomas's Hospital, 1899.

in the latter family it will be noticed that in the childship of eight children there are only two abnormals.

This comparative absence of abnormals is important

in another respect, in that it often becomes difficult or even impossible to trace the source of a defect in a family.

For instance, in the Ichthyosis family (Fig. 14) we only know for certain that the defect has been transmitted indirectly through one of the grandparents, but in the following family (Fig. 15) we have definite information of transmission of the Ichthyosis from an abnormal female in the first generation.

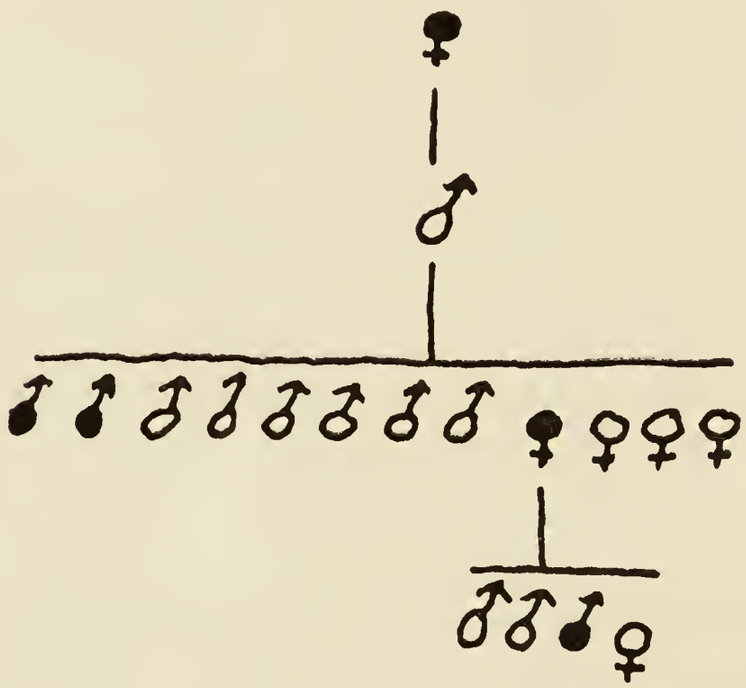


Fig. 15. Ichthyosis.
T. F., St. Thomas's Hospital, 1902.

On the other hand, when we turn to another family (Fig. 16) tainted with Tylosis, we find an abnormal male in a childship of ten children, but we cannot be sure that he received his defect by indirect transmission, for its presence may equally well be explained by spontaneous origin.

Indirect transmission for this reason cannot always be relied upon as a ready explanation of the appearance of

a defect in a childship, and care has to be exercised that its influence is not overrated.

The question as to how, with indirect transmission, the reduction in the numbers of the abnormals can be brought about, is seemingly not a difficult one to answer.

The carrier clearly takes the place of an abnormal in a childship, so that the reduction is brought about by the actual substitution of abnormals by carriers.

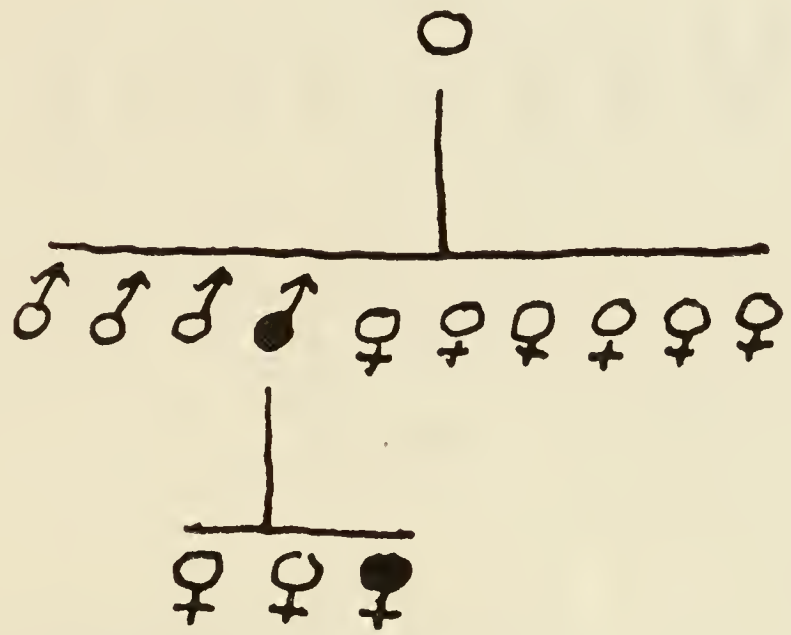


Fig. 16. Tylosis.
Private Case, 1900.

A childship of eleven children in the second generation of the Cerebellar Ataxia family (Fig. 12) may be considered as a case in point.

With common direct transmission we should expect about one-half of the children to be bearers, but here only about one-quarter are bearers.

If, however, the two carriers are considered as substitutes for bearers, the influence of inheritance on the childship affects five children, or about one-half of the childship.

The influence of heredity as seen in direct transmission may therefore be considered as still alive in indirect

transmission, though masked by the substitution of bearers by carriers.

We can then picture to ourselves the division of a childship into two halves, each half showing the influence of one parent in transmitting a given defect, and in com-

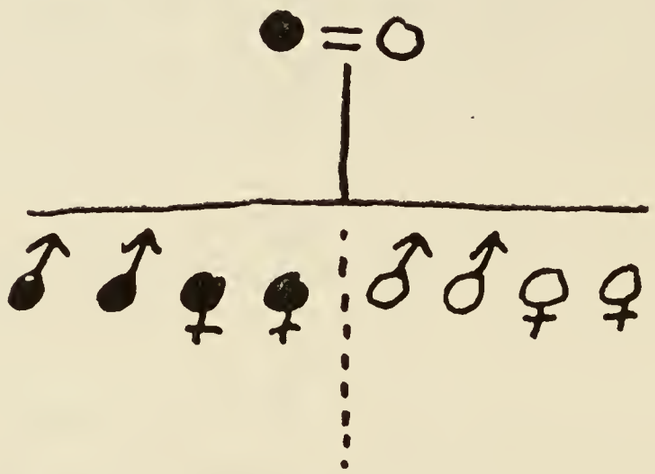


Fig. 17.

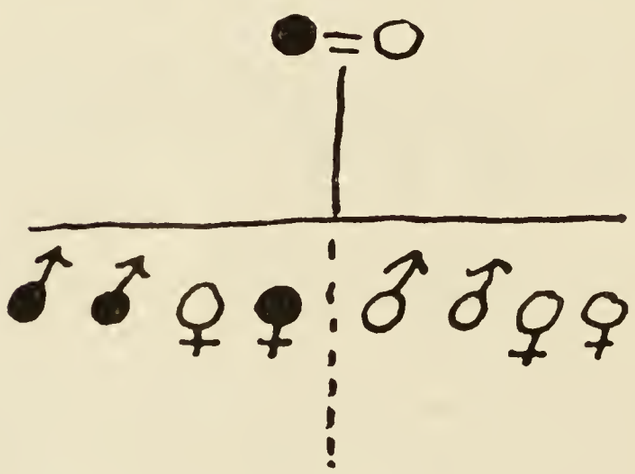


Fig. 18.

mon direct transmission (Fig. 17) the dividing line will merely separate the abnormals from the normals.

If a carrier appears in such a childship the chances are greatly in favour of a female carrier taking the place of one of the abnormal females (Fig. 18), for females, as already stated, act as carriers far more frequently than males.

The appearance of these female carriers in families

produces a remarkable change in the character of the transmission, and this change is undoubtedly due to a marked peculiarity of the carrier female, for if she once appears she tends to become permanently established in a family.

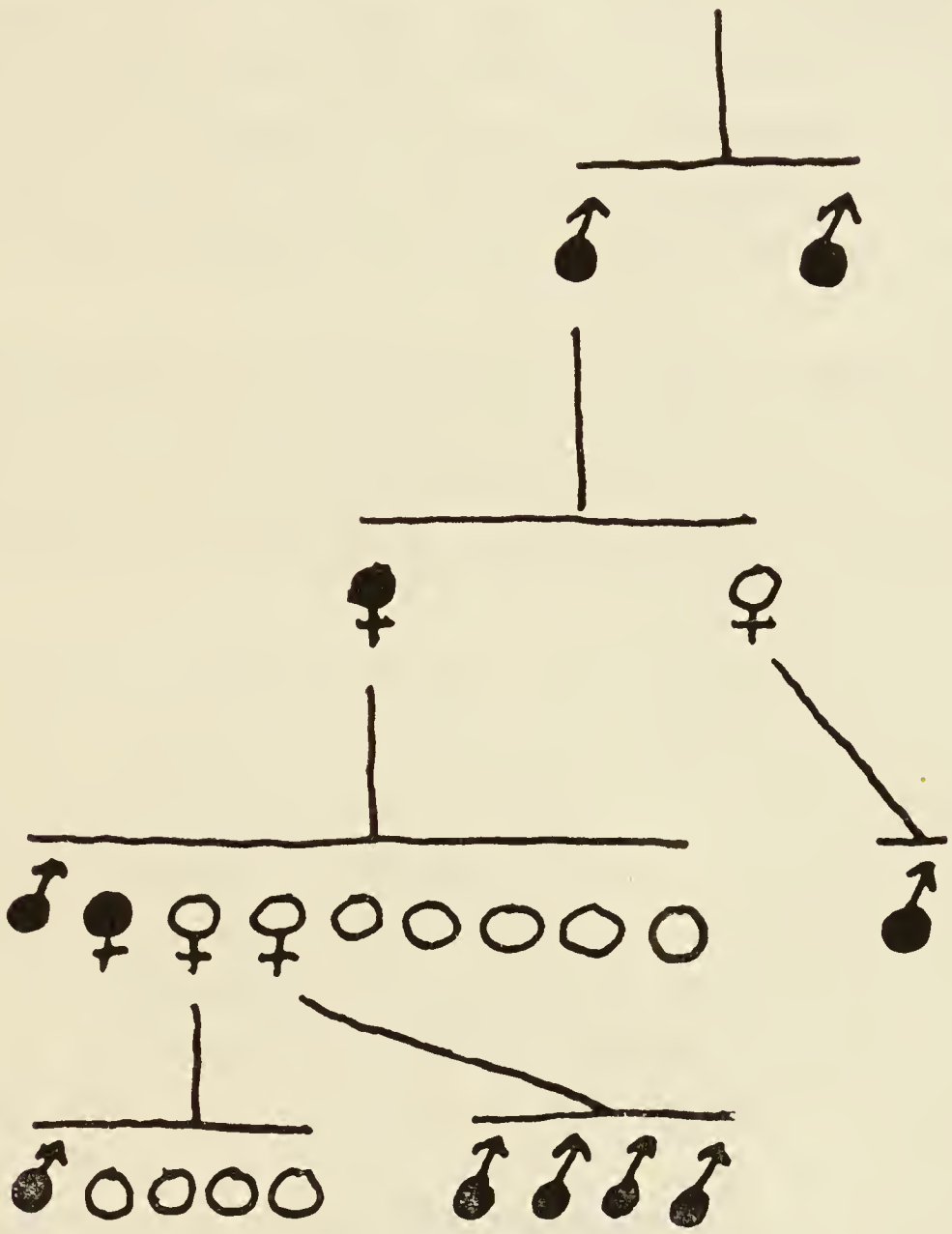


FIG. 19. POLYURIA.
Gee, *Bart.'s Hosp. Reports*, 1877.

The abnormal female who with direct transmission is much in evidence therefore shows signs of becoming a vanishing quantity with indirect transmission, and her place tends to be occupied by a carrier female.

The necessary result of this change is that the abnormal males begin to appear relatively in much greater numbers,

and the carrier female becomes quite a feature of the transmission pedigree.

Gee's family (Fig. 19) is interesting in this respect, for there are only two abnormal females as against nine abnormal males, and it should be noted too, that both of the abnormal females have carrier sisters who have passed the defect on to their sons. Here, then, we seem to have a beginning of the carrier female type of transmission in a family in which there are still some abnormal females and still some traces of ordinary direct transmission.

The pedigree from Snell dealing with Retinitis Pigmentosa (Fig. 20), whilst giving a similar scarcity of abnormal females, is still more instructive in showing how the change from female bearers to female carriers must affect the type of transmission.

In the second generation a carrier female is transmitting the disease to three sons and one daughter, and this daughter in her turn is found to be transmitting directly only to her sons. If this abnormal daughter had been a carrier, her branch of the family would have displayed the typical carrier female type of transmission.

Although she is an abnormal, the result in her own childship is exactly the same as if she had been a carrier.

We can well understand, therefore, that if abnormal females can disappear from families only to be replaced by carrier females, the change in the character of the transmission will be in the direction of transmission through carrier females with the males only being affected.

In these families in which abnormal females are disappearing the increase in the number of carrier females necessarily must cause direct transmission to be less frequent, and it is obvious that if direct transmission

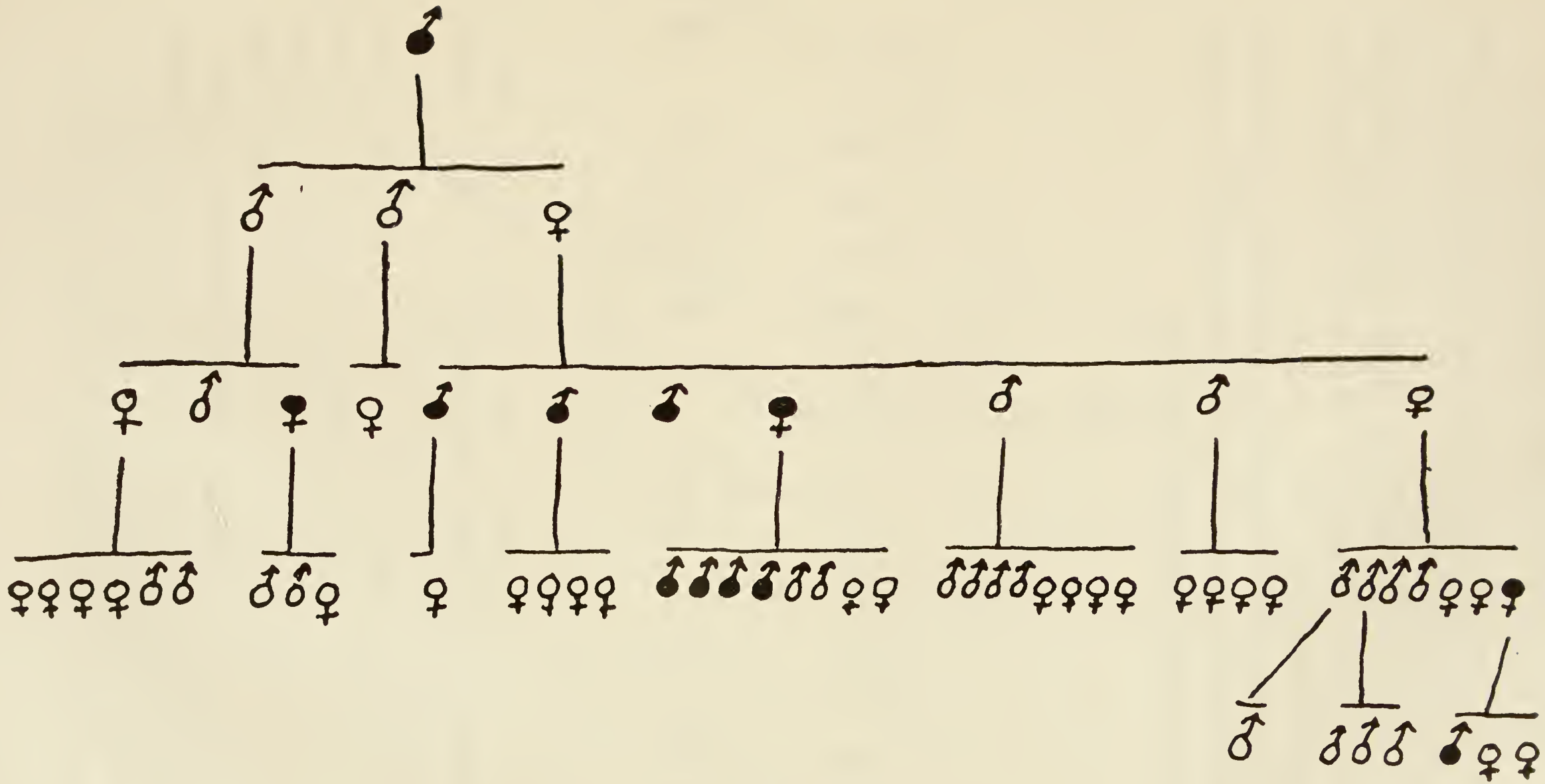


FIG. 20. RETINITIS PIGMENTOSA.
Simeon Snell, *Trans. Ophth. Soc. U.K.*, vol. xxvii, 1907.

occurs the males must, as bearers of the defect, be the more responsible agents.

A glance at Nettleship's pedigree of a colour-blind family settles at once the form in which the direct transmission must exist.

If the one abnormal female in this family is replaced by a carrier female, the male in the first generation will only be transmitting directly to his sons.

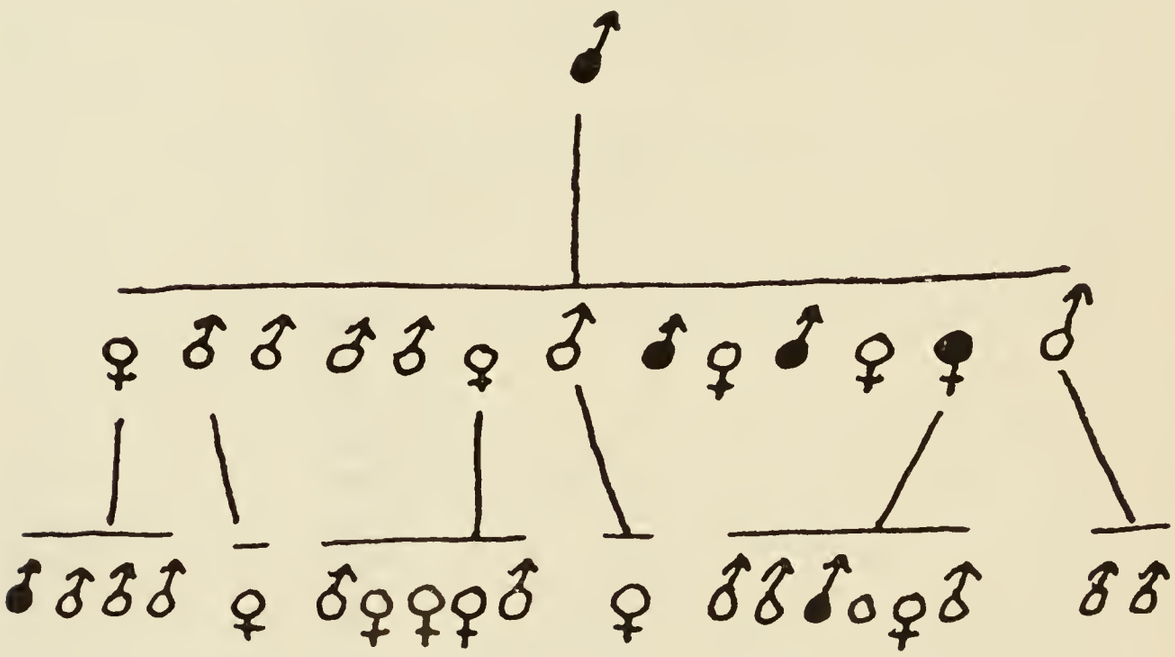


FIG. 21. COLOUR BLINDNESS.
E. Nettleship, *Trans. Ophth. Soc. U.K.*, vol. xxvi, p. 255.

We are thus able to contemplate a final stage of transmission in which the abnormal female has entirely disappeared.

The pedigree-formula (Fig. 22) will now be a simple one, for males will only be transmitting directly to males and females will only act as carriers to transmit to their male children. This stage of transmission is clearly closely related to, if not identical with, the carrier female type of transmission, for it will be noticed in the pedigrees brought forward to illustrate this type (Figs. 3–9), that abnormal males here and there transmit directly to their sons.

This direct transmission cannot often occur with the more severe defects, but it can nevertheless be a pronounced feature when marriages are not checked (Figs. 23, 24, 25).

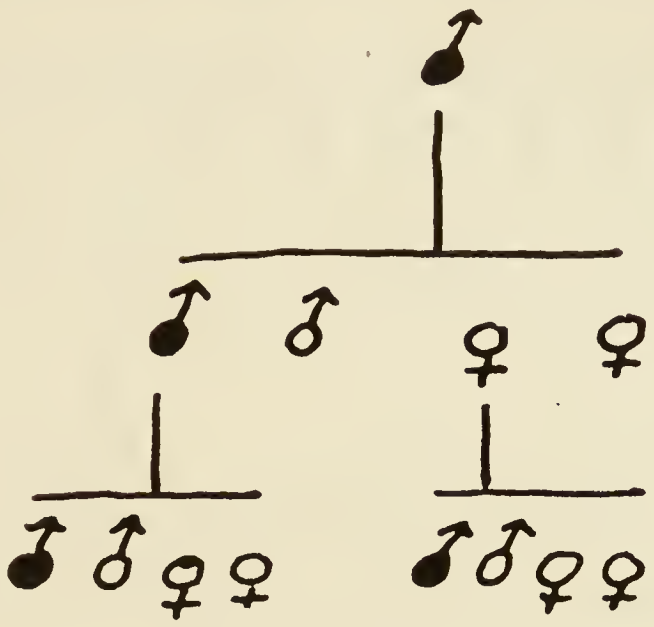


FIG. 22.

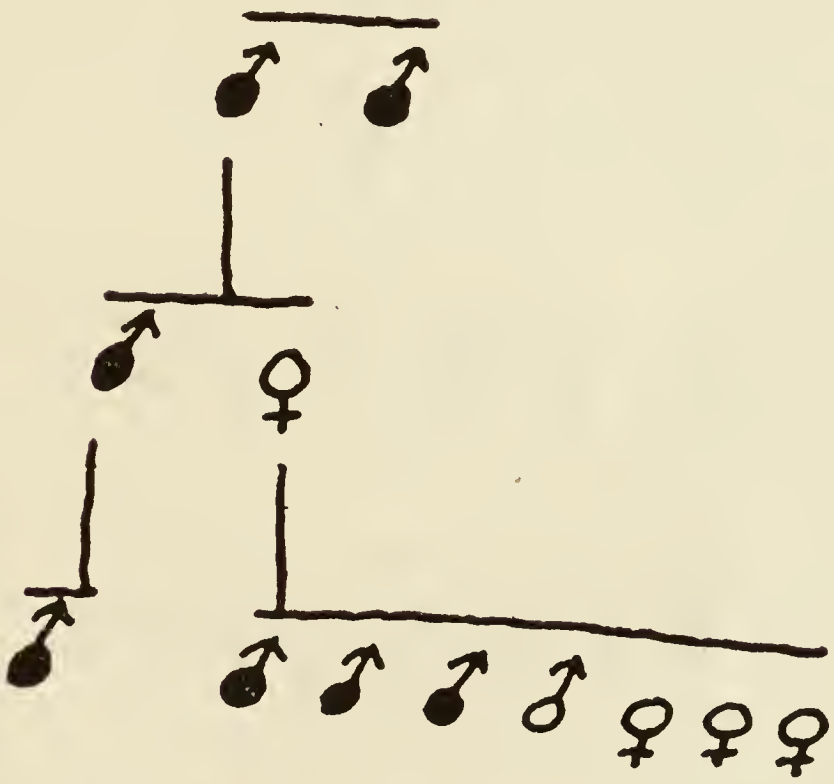


FIG. 23. COLOBOMA IRIDIS.
Streatfield, *Ophth. Hosp. Rep.*, 1858, p. 153.

In these families the abnormal males are very much in excess of the normal males, but this excess is probably a chance one, which cannot be considered in any way characteristic of this type of transmission.

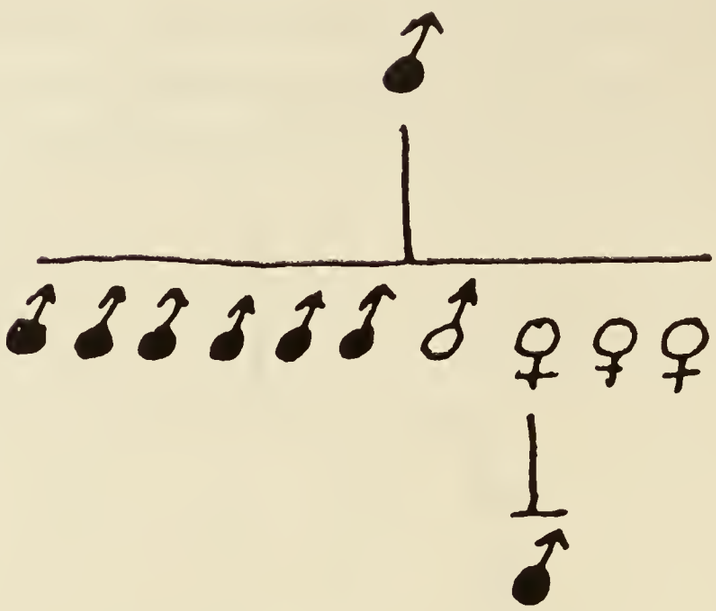


FIG. 24. COLOUR BLINDNESS.
Frost, *Ophth. Soc.*, April 7, 1881 ; *Lancet*, 1881, p. 663.

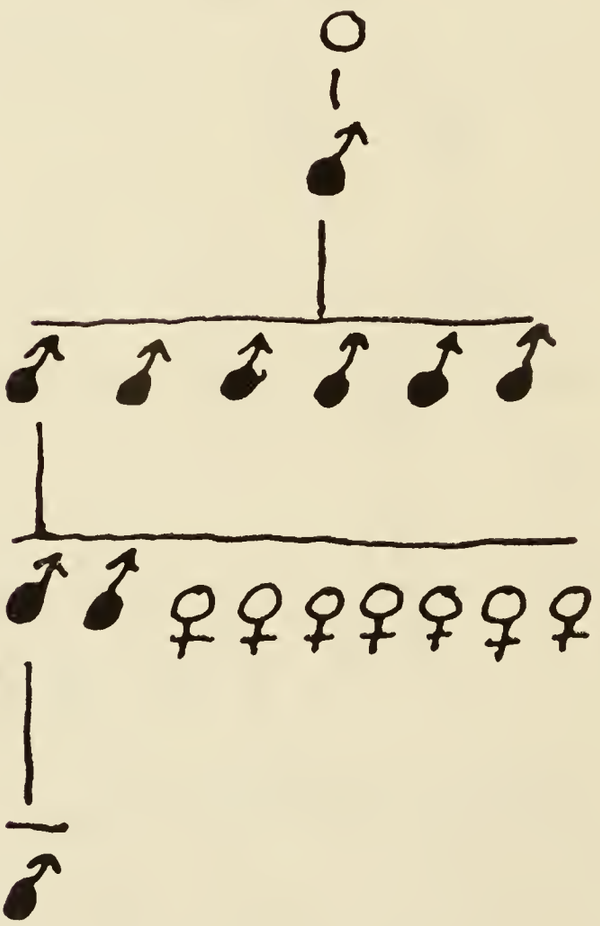
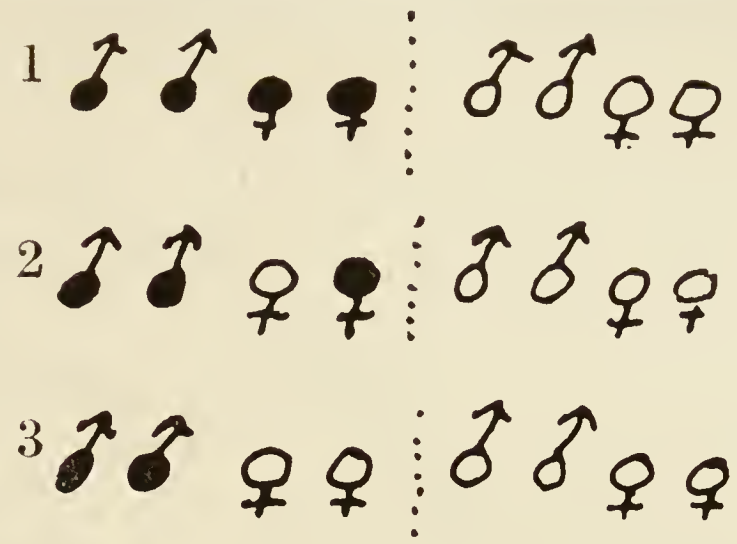


FIG. 25. ICHTHYOSIS.
The Lambert Family, *Phil. Trans.*, 1731, p. 299 ; 1755, p. 23.
Mémoire sur les Frères Lambert, *Mém. de la Soc. des Sci. de Strasbourg*, tome i, p. 327, 1811.

With the gradual disappearance of the abnormal females, the childship, as far as we can judge, passes through the following stages :



and an interesting question arises as to whether or not the proportion of affected males can ever be on the average less than that found in the third stage.

Although in some families we find the abnormal males and carrier females apparently failing to transmit to any extent, we are hardly justified in coming to a definite conclusion on this point.

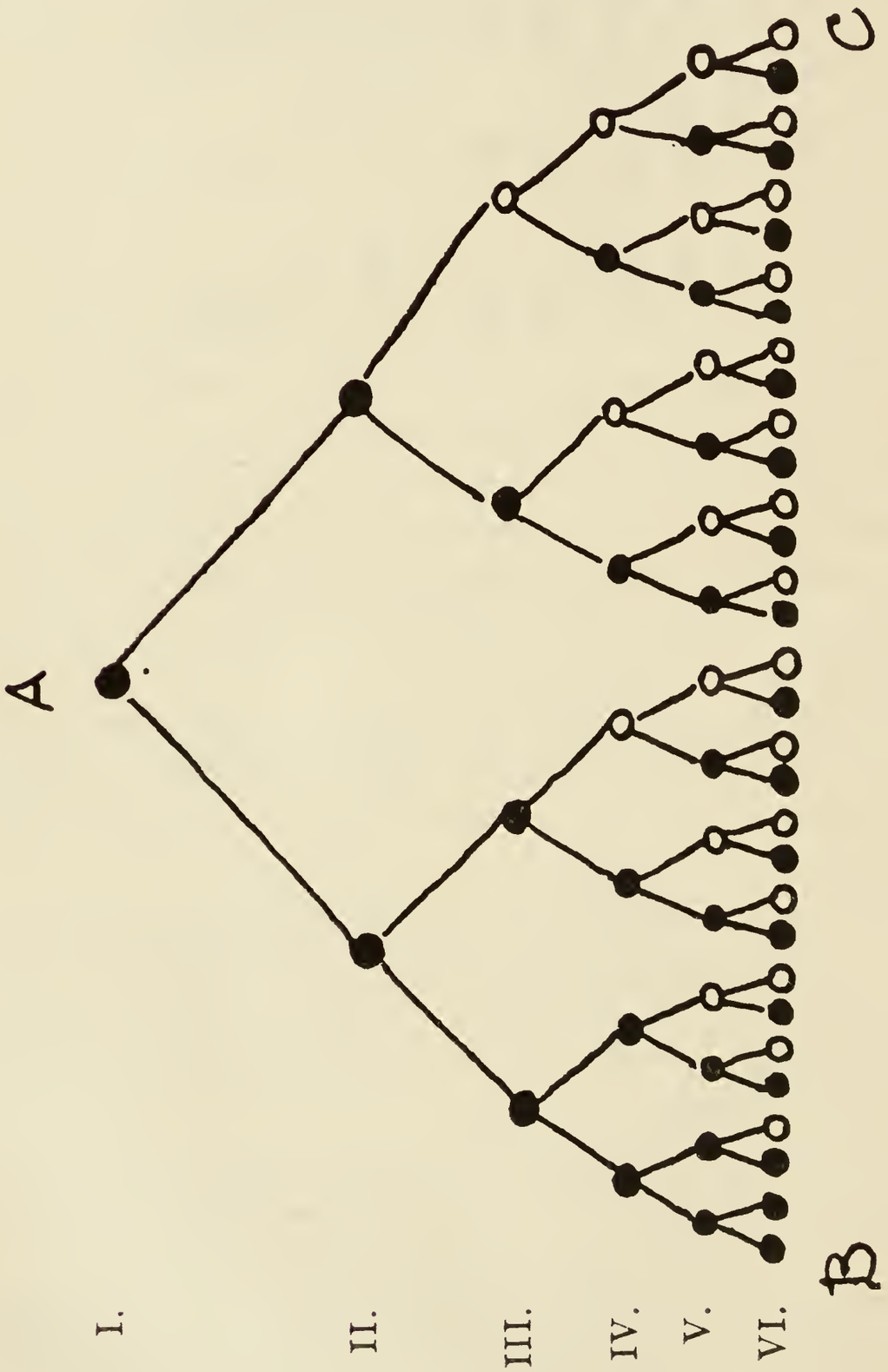
It is quite possible, however, that the abnormal males may eventually in some cases become carriers themselves, in which case the defect would tend to disappear completely from the family.

With the completion of the series of pedigrees showing the gradual disappearance of the abnormal females, the evidence seems to give support to the theory that all types of transmission are evolved in the first place from common direct transmission.

This theory is of great importance in one respect, for with it it is possible to formulate a general scheme which will embrace all the facts of hereditary transmission.

Supposing that in an imaginary family carriers appear in certain branches and tend to become established as such in subsequent generations.

If we omit altogether the normals who, strictly speaking, have nothing to do with the transmission of a defect, we can sketch out the following pedigree scheme, which therefore deals only with bearers and carriers.

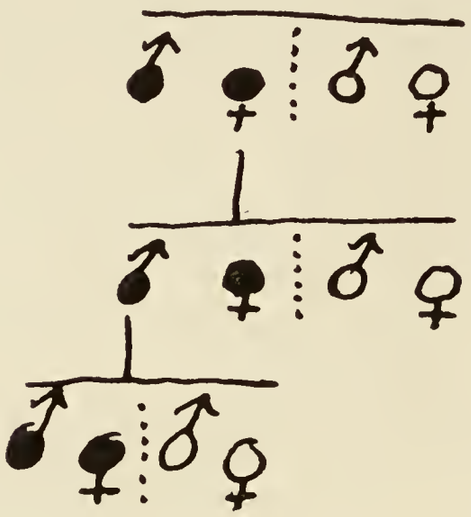


In the second generation the absence of carriers shows that there has been common direct transmission, but in the third generation a carrier takes the place of a bearer in the line of descent AC, with the result that similar carriers continue to appear in all childships directly descended from this carrier. In the same way carriers will be seen gradually appearing in other branches of the family in the fourth, fifth, and sixth generations, and these again will cause carriers like themselves to appear in all subsequent generations.

The defect which is inherited by an individual at A will in the line AB always be transmitted directly from parent to child, whereas in the line AC it will eventually always be transmitted indirectly through a carrier parent to the child.

The line AB will express continuous direct transmission with an absence of carriers,

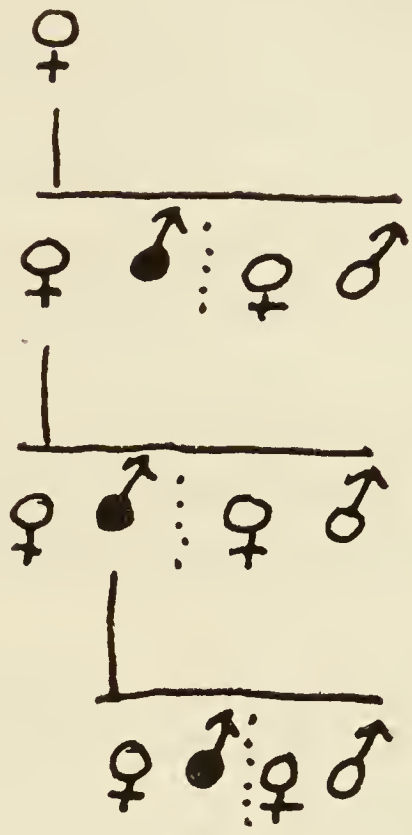
and therefore represents common direct transmission which by expansion becomes:



The line AC as a direct contrast expresses continuous indirect transmission,

and owing to the fact that it shows the longest continuous line of carriers, it will be the first line of descent to show the influence of carrier females on the change of the type of transmission.

The continuation of the line AC may therefore be taken to represent the carrier female type of transmission, which by expansion becomes :



The extreme branches of the hypothetical family, AB and AC, will then represent the extreme types of transmission, namely common direct and carrier female, and all families tainted with a defect may be looked upon as an integral part of the scheme, so that the type of transmission prevalent in any given family will depend on the relative position of the family in the scheme.

The lines of descent between the points B and C will in this way represent families in which the type of transmission is being gradually changed by the appearance of carriers.

So far we have only considered the female carrier, but the influence of the male carrier on the type of transmission is by no means a negligible quantity.

The male carrier when he first appears in a family undoubtedly transmits to both his male and female chil-

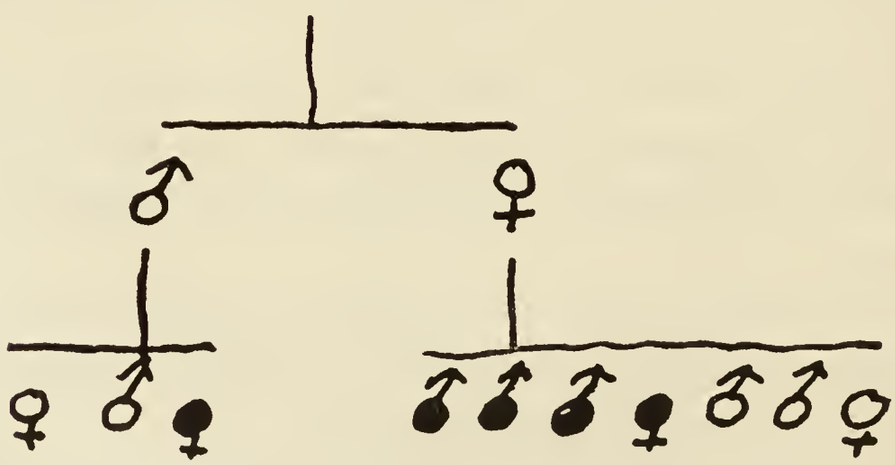
dren just in the same way that a carrier female does under similar circumstances. If his influence in changing the type of transmission is clearly insignificant in comparison with that of the female carrier, it nevertheless seems to make itself felt now and again. We have suggestions here and there in our pedigrees that the male carrier is responsible for the limitation of a defect to the females of a childship just in the same way that female carriers become responsible for the limitation of a defect to the males.

There is, however, no tendency for a long line of carrier males to become established in a family, and in this respect the male carrier differs greatly from the female carrier.

The male carrier is in fact an unstable quantity in transmission, due, no doubt, to his failure to produce male carriers like himself.

Examples of limitation of a defect to the females of a childship are therefore comparatively rare, and there is a striking absence of families showing a carrier male type of transmission.

In Snell's Retinitis Pigmentosa family (Fig. 20) a male carrier is seen to be transmitting to his daughter,



RETINITIS PIGMENTOSA.
Simeon Snell (see Fig. 20).

and again in the case of two first cousins suffering from a muscular atrophy we have the following interesting pedigree:

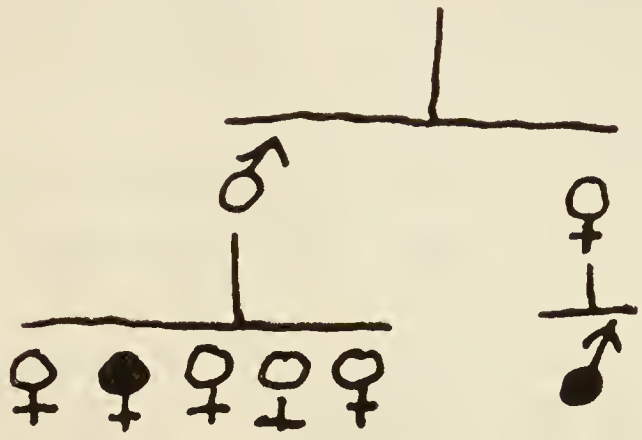


FIG. 26. MYOPATHY OF THE LANDOUZY-DÉJERINE TYPE.
J. Taylor, *Proc. Roy. Soc. Med.*, vol. i, No. 1, November 1907.

It may be mentioned too that Ichthyosis limited to the females of a childship, although rare, is a recognized peculiarity of the disease, and the following family shows transmission through the father to three females.

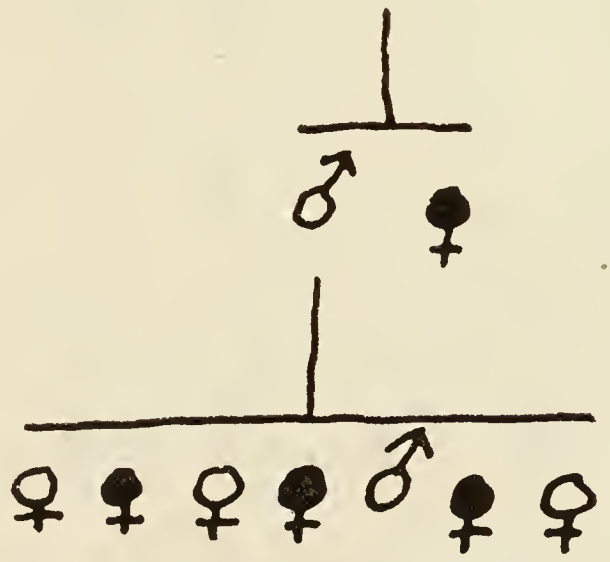


FIG. 27. ICHTHYOSIS.
L. B., St. Thomas's Hospital, 1908.

It must be admitted, however, that these examples can hardly be considered as satisfactory evidence, but at any rate they are suggestive.

One more possible feature of the limitation of a defect

to females is that of direct transmission from female to female, which would correspond to the direct transmission from male to male found with carrier female transmission.

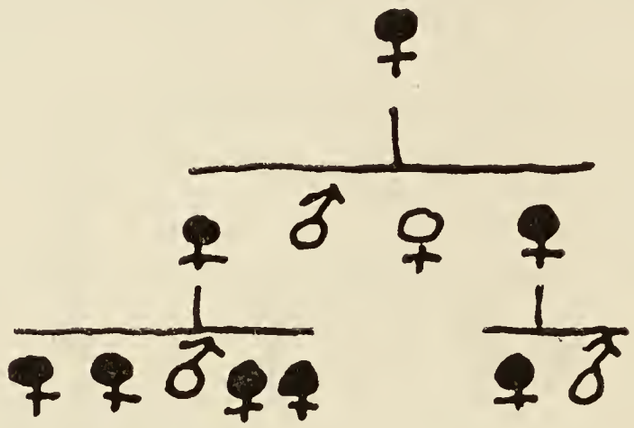


FIG. 28. HELICAL FISTULAE AND ACCESSORY AURICLES.
J. Howell Evans, *Proc. Roy. Soc. Med.*, vol. ii, No. 3, p. 102.

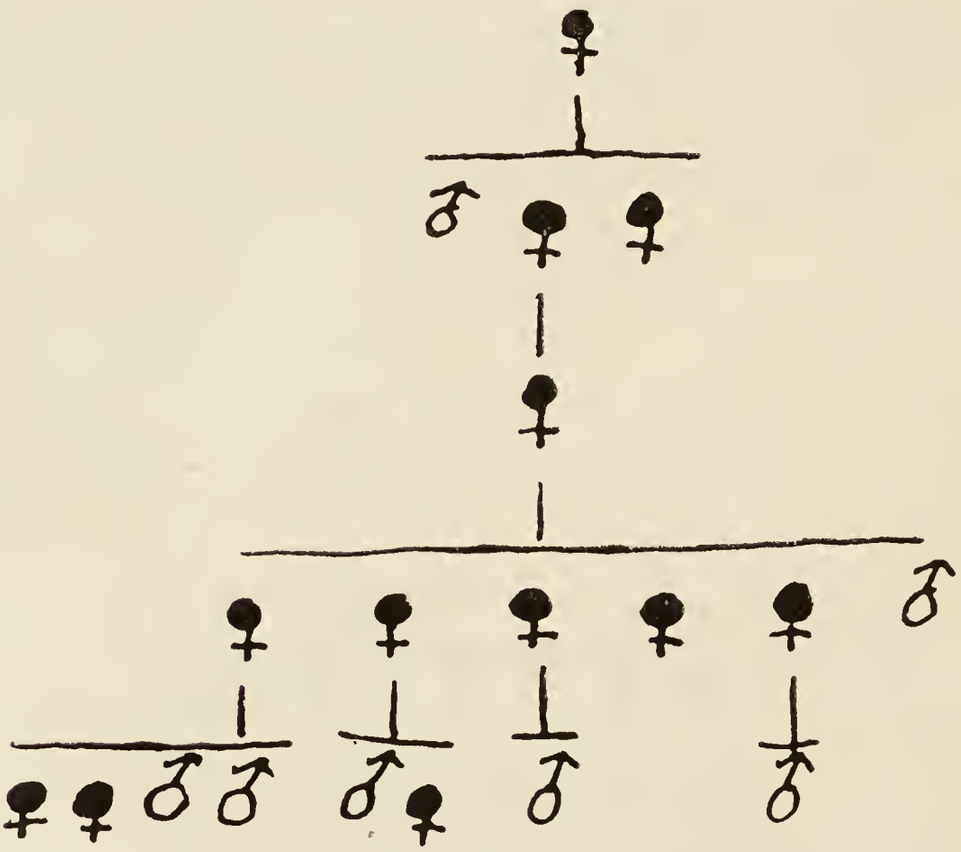


FIG. 29. COLOUR BLINDNESS.
Cunier, *Annales d'Oculistiques*, i, p. 417, 1839.

Two families (Figs. 28, 29) show this direct transmission, but considering the minority of the males in the childships

it would be unwise to assume that with more equal proportions of the sexes there would still be absence of affected males. The same difficulty arises in the case of Ballantyne's family (Fig. 30), for with regard to the disease 'there was a tradition that it had been in the family for generations, but that it affected only female members and only some of them ; that it was only transmitted through the female members, and that it usually skipped a generation'.

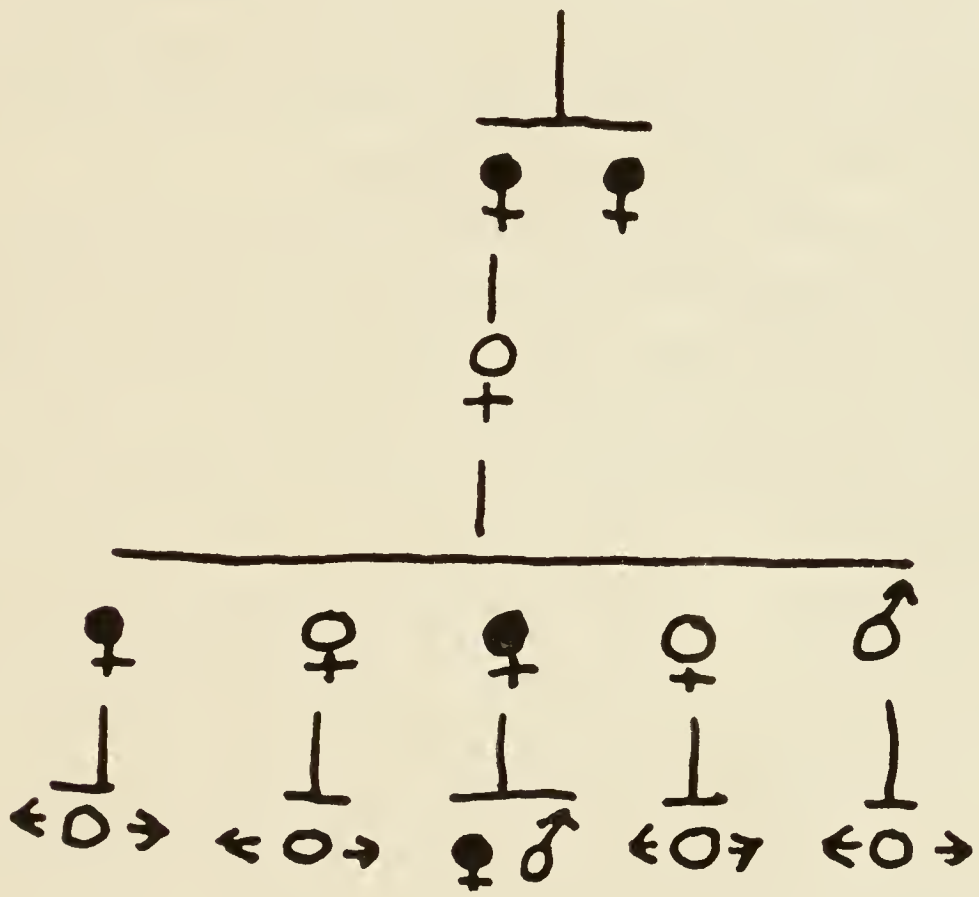


FIG. 30. TYLOSIS PALMAE ET PLANTAE.
Ballantyne, *Pediatrics*, 1896, i, p. 337.

Here again the pedigree gives us but little information concerning the males, but it is quite possible in this and in other families that males are actually in a minority, in which case only the females would appear to be responsible for both direct and indirect transmission.

The influence of the male carrier cannot therefore be compared with that of the female carrier.

Taking a broad view of the facts of transmission, we feel justified in the belief that we are dealing with a general process which may be called the Natural Elimination of defects. When a defect begins to interfere with marriage it must either disappear from a family or be transmitted indirectly to future generations. The female as a carrier plays the chief part in this indirect transmission, and in doing so brings about a permanent reduction of the relative proportion of abnormals owing to the disappearance of the abnormal females.

An abnormal male is left who can transmit the defect to his sons and daughter's sons, but this is not necessarily the end of the story of transmission.

There is some evidence which leads us to think that these abnormal males may sometimes be unable to transmit directly to their sons, and if this with further research proves to be correct, the total elimination of the defect from the family bids fair to become eventually an accomplished fact.

HEREDITARY TRANSMISSION AND THE PRINCIPLES OF MENDEL

The idea that somatic characters are represented in the germ-plasm by independent units is largely based on our experience of particulate inheritance.

'I assume,' says Weismann, 'that the germ-plasm consists of a large number of different living parts, each of which stands in a definite relation to particular cells or kinds of cells in the organism to be developed, that is, they are "primary constituents" in the sense that their co-operation in the production of a particular part of the organism is indispensable, the part being determined both as to its existence and its nature by the predestined particles of the germ-plasm. I therefore call these last Determinants, and the parts of the complete organism which they determine Determinates, or hereditary parts.'

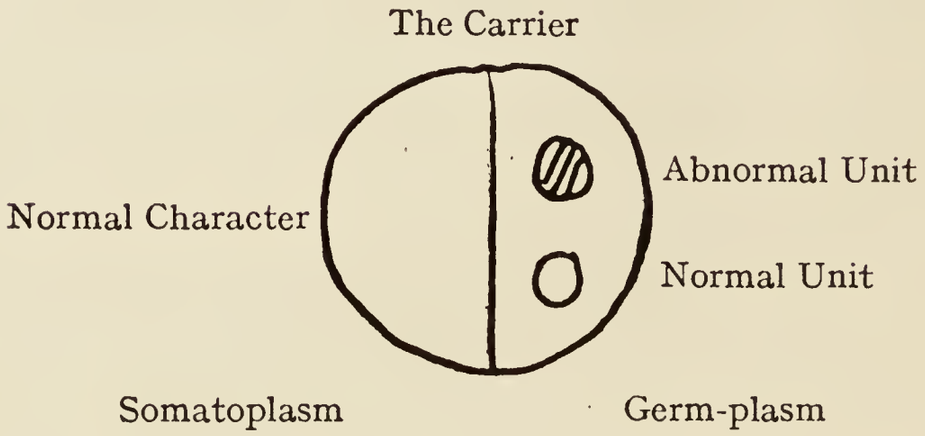
This interesting passage from *The Evolution Theory*, which brings out so clearly the idea of transmission by germ units, is followed by another passage which draws attention to a case in point.

'Thus, for instance, in many human families there occurs a small pit, hardly as large as the head of a pin, in the skin of the ear, whose transmission I have observed from the grandmother to the son and to several grandchildren.

'In such a case there must be a minute something in the germ-plasm, not present in that of other human beings, which causes the origin, in the course of development, of this little abnormality in the skin.'

If this principle of unit representation be applied in

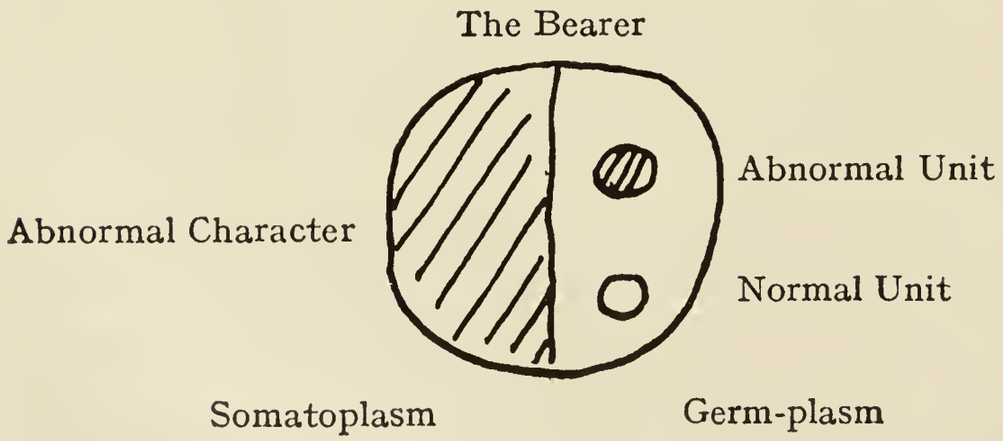
the case of the carrier, we at once find ourselves obliged to uphold the doctrine of transmission by dual germ units which is the fundamental principle of Mendelian Inheritance.



The carrier is an individual with a normal somatic character, which is represented in the germ-plasm by a corresponding normal unit. The germ-plasm, however, is known to carry an abnormal unit, from the fact that the defect can be transmitted to the next generation.

Here, therefore, in the germ-plasm we have two dissimilar units, and transmission will be dependent on the future movements of these two units during the development of reproductive cells from the germ-plasm.

The carrier therefore satisfies the first postulate of Mendelian inheritance, namely Transmission by Dual Units.



If the bearer carries in the germ-plasm such a pair of dissimilar units, it is obvious that the abnormal unit must have exerted an active influence on the formation of the abnormal somatic character, an influence which by some means or other would be inoperable in the case of the carrier.

Owing to the fact that in common direct transmission the abnormal unit, if present, always determines the presence of an abnormal somatic character, it is usually claimed that this abnormal character is a true dominant character in the original Mendelian sense.

It is clear, however, that the defective character ceases to be dominant in the case of the carrier, for the normal unit asserts itself for the determination of a normal character.

This fact seems to be rather a stumbling-block to the practical Mendelian, who from his experiences with animals and plants tends to divide his characters into two classes of dominant and recessive.

The peculiar position of the carrier in transmission forces him to the conclusion that a character such as Haemophilia must be dominant in males and recessive in females.

That such a conclusion is erroneous, is obvious when we consider the essential nature of the so-called dominant character. These characters, when purely structural, are invariably an expression of cellular growth which is present in one parent and absent in the other. The dominant character therefore represents a positive cellular growth, whereas the recessive character denotes an absence of this growth.

A crossing of two characters by hybridization leads to a blend of these characters in the somatoplasm, provided that both characters are able to assert themselves to their

fullest extent. A common result of this crossing is that the hybrid displays a character which is partly paternal and partly maternal (Fig. 31). If, however, one parental character is dependent on a positive growth value which

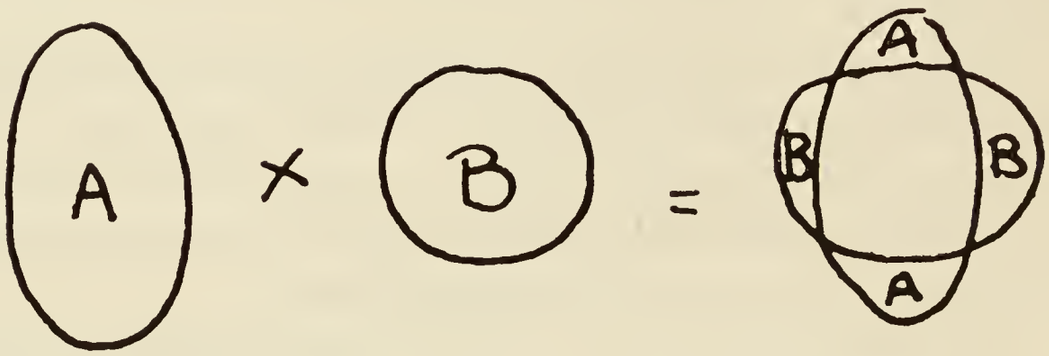


FIG. 31.

is wanting in the case of the other parental character, a blend between the two characters would result in the disappearance of the weaker character (Fig. 32).

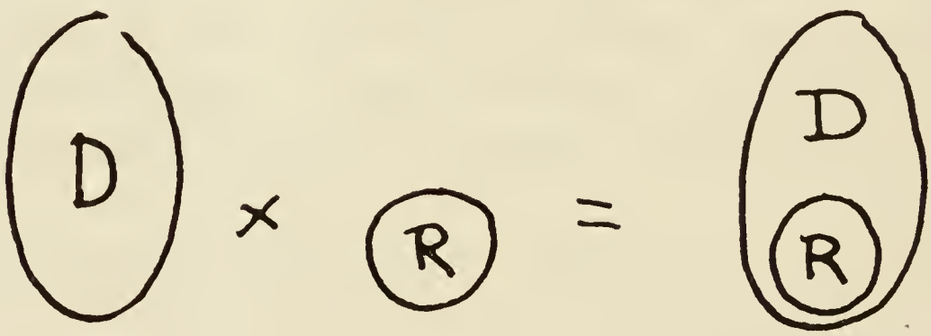


FIG. 32.

The hybrid character under these circumstances, while still being a blended character, would to all appearances be identical with the greater of the two original parental characters.

Dominance of a character from this point of view is a question of cellular growth, and denotes a fixed relation to a recessive character which cannot be changed under

any circumstances. It would be a physical impossibility, therefore, for a character to be dominant in one individual and recessive in another.

It may be quite true that several defects behave like dominant characters say in common direct transmission, but it may well be asked if these defects have any right to be called dominant characters.

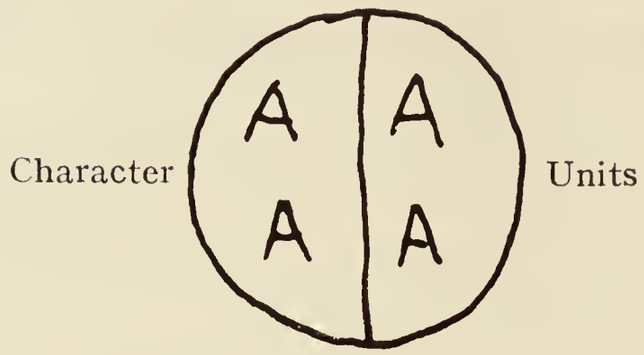
An increase in the number of fingers is essentially a dominant character, but a reduction in the number of digits from the absence of bones can hardly be claimed as a true dominant character. Both of these defective conditions are, however, commonly handed down by direct transmission so as to apparently satisfy the Mendel formula, DR × RR = DR.RR, and for this reason are both considered to be dominant characters.

It is a striking fact that the majority of human hereditary defects are truly defects in that there is a something wanting, and in this sense they cannot with any justification be considered as dominant characters.

The fact remains that defective characters in some families always appear in the body if they have representation in the germ-plasm, whereas in other families they do not always appear in the body in spite of being represented in the germ-plasm. The problem which we have to solve in man is thus not one of dominance of characters, but the more important one of the crossing of defective units from the germ-plasm to the somatoplasm. We will now turn to the more obvious possibilities of this important function of the units, and consider with the aid of diagrams the units which *are* present in the germ-plasm and which *have* entered the somatoplasm to form the somatic character.

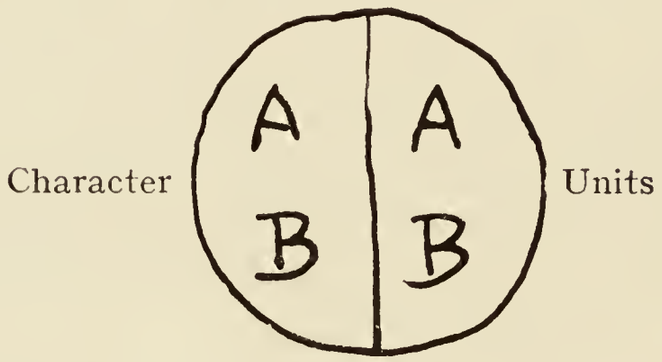
I. Both units may enter the somatoplasm with a varying result dependent on the nature of the units.

(A)



If the dual units A and A are similar, the individual must exhibit the character A, which is in reality a blend of A and A.

(B)



If the dual units are dissimilar, the character AB will be either all A or all B, if either A or B is dominant in growth value. If neither A nor B is dominant, the character will as a blend show something of A and something of B.

On the supposition that one of the units represents a defect, AB as a blend would be a defective character, but a varying one owing to a chance preponderance of either A or B.

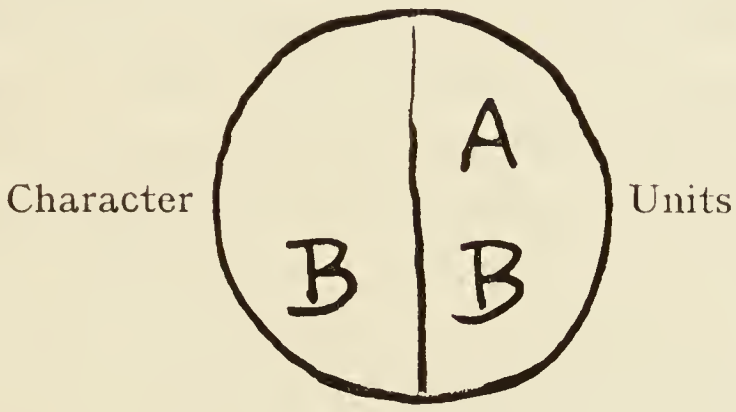
Now it happens that in families tainted with defects the abnormal individuals do not display identical but varying degrees of the same defect, sometimes to a marked extent.

We may conclude, therefore, that a defect, when

observed as a varying quantity in a family, is a blended character due to the crossing of dissimilar units into the somatoplasm.

On the other hand, uniformity in the degree of a defect would be due either to dominance of cellular growth or to the crossing of similar units into the somatoplasm.

II.



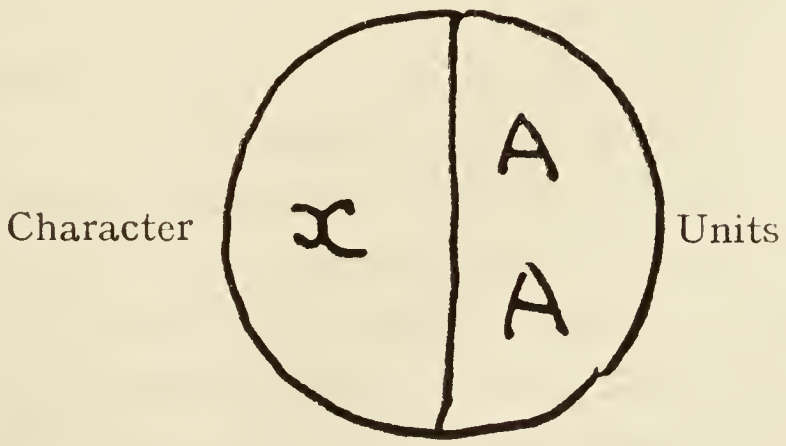
One only of the two units may take part in the formation of a somatic character.

The carrier of a defect may be considered as a case in point, if A represents a latent defective unit and B the normal unit which has entered the somatoplasm.

The fact that an abnormal unit can be latent in one case does not exclude the possibility that one of two normal units may be latent in other cases.

The individual would then be a carrier of a normal character.

III.



Neither of the two units may take part in the formation of a somatic character.

This possibility must be admitted if single units, whether normal or abnormal, can be latent, and should be realized more especially as a result of consanguineous marriages.

The somatic character under such circumstances would be a negative character due to the absence of the character represented by the latent units.

Certain rare diseases, only found in childships, may possibly in this way owe their origin to the absence of a normal character. Albinism, too, may in some cases be due to the inherited latency of two normal colour units.

With this rather formidable array of possible individuals who can take part in hereditary transmission, Mendelian inheritance can hardly be expected to be a simple process.

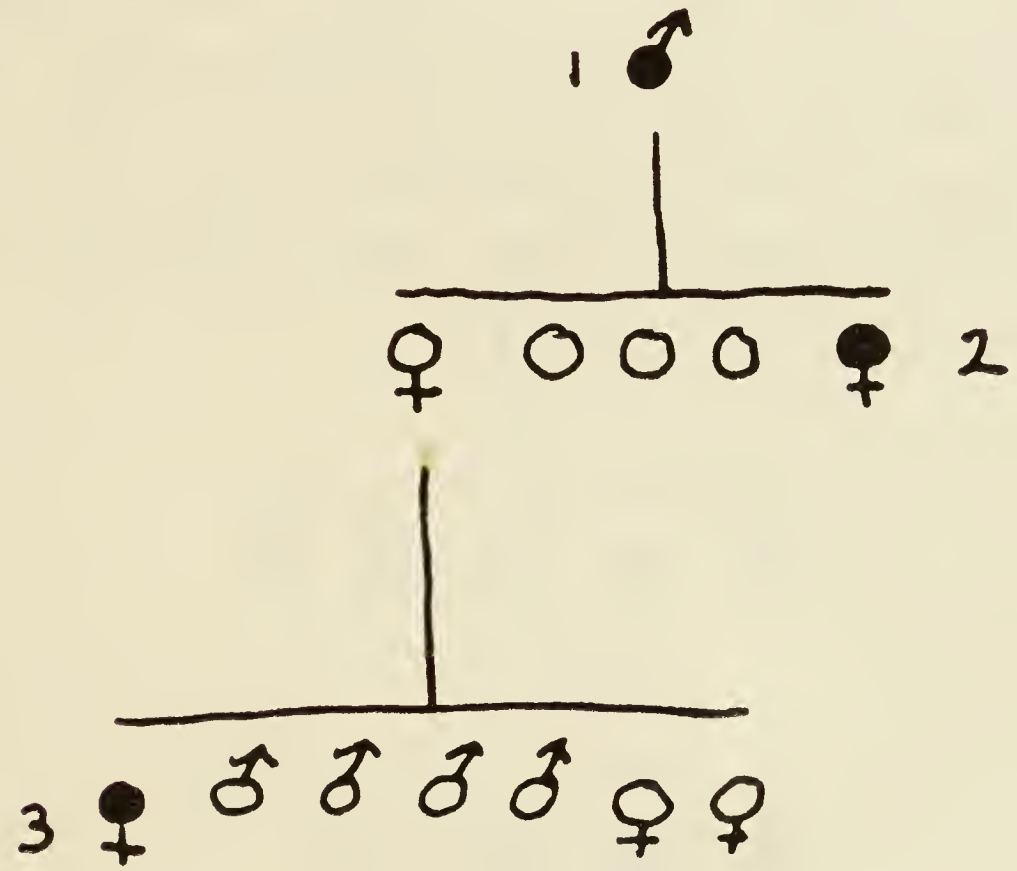
The question as to how far the principle of transmission by dual units is supported by the actual facts of inheritance still remains to be answered, and this is by no means an easy matter. The necessity of dealing with large numbers of families for statistical purposes is obvious, but there are many difficulties to be faced.

Pedigrees recorded in the past have in many cases been published merely to show the relationship of the abnormals, and consequently the normal members of the family have been left out of consideration unless they happen to take part in the transmission as carriers.

Of late there has been a movement in the direction of more careful records, but it must be allowed that a true history of inheritance is exceedingly difficult to obtain except by prolonged research. The chief difficulty seems to be the verification of statements made concerning the reputed defects of more distant relations. For some defects the verification may be comparatively easy, but for others there is the question of differential diagnosis to be considered, and this inevitably makes errors possible, especially with an observer with biased opinions.

For instance, if a family is tainted with a severe form of Haemophilia, death from haemorrhage is a common event which can hardly escape notice, whereas if the Haemophilia exists in only a mild form much evidence is required before a member of a family can be pronounced as abnormal.

The following brief notes on two families are interesting in this respect :—



HAEMOPHILIA.
St. Thomas's Hospital, April 1899.

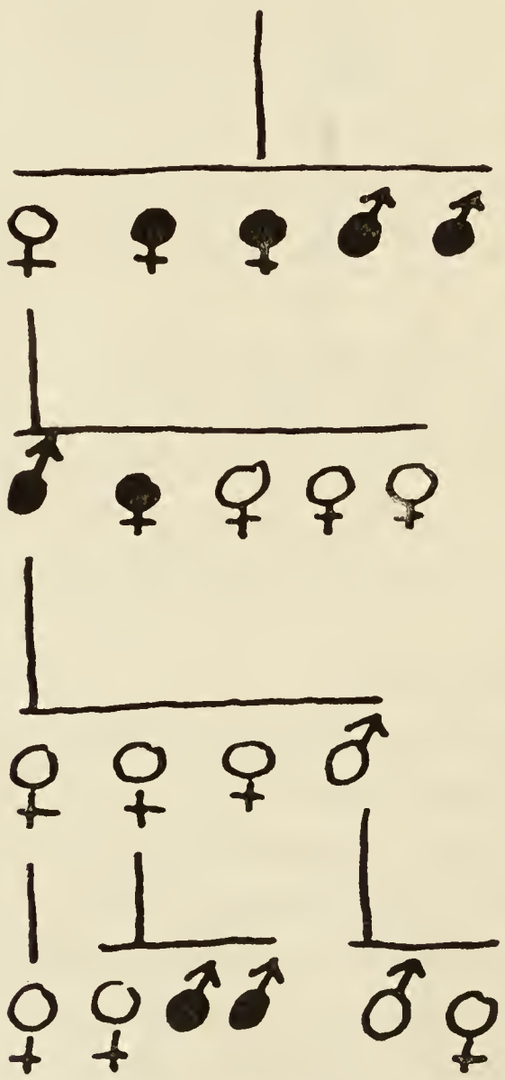
1. Had Epistaxis often.

2. Had profuse menstruation commonly. Haemorrhage after having a tooth pulled out.

3. F.V., æt. 22. Anaemic-looking. Had Epistaxis now and again. Menstruation profuse, often lasting eight days. Bruised very easily (large bruises) at slightest cause. Had cut fingers on two occasions and had prolonged haemorrhage. Relations would not allow her to have teeth pulled out, as they feared haemorrhage.

Had double ovariotomy performed, April 20, 1899, by the late Dr. Cullingworth, for ovarian cysts.

The cysts on each side were filled with a quantity of soft, sticky blood-clot and fluid-altered blood. There was nothing in the way of twisted pedicles, &c., to account in any way for this haemorrhage. No special haemorrhage at operation, but perhaps there was more oozing from abdominal wall than usual. Was very bad after the operation, and infusion was necessary. Made a complete recovery. Had a few small haemorrhagic spots on thighs when still in bed, but a week after getting up legs were simply covered with minute purpuric spots with a few scattered about the arms and trunk. Never had pains in joints.



HAEMOPHILIA.

B. H. Kingsford, *Brit. Med. Journ.*, August 29, 1908, p. 545.

Dr. Kingsford draws attention to this family because of the death of a haemophilic boy from an uncommon form of intussusception. The family history given is as follows :—

> 'His maternal great-grandmother was healthy, but both her sisters died from haemorrhage in confinements, and both her brothers died from haemorrhage. She had five children—four daughters, one of whom died from haemorrhage in her sixth confinement, and another died from " change of life " ; and one son (patient's grandfather), who, during the first thirty years of life, was a " bleeder ". He had one son and three daughters (one of whom was patient's mother), none of whom suffered from Haemophilia. The patient had one brother, a marked haemophilic, and one sister healthy.'

It is obvious that in the case of these two families the observer must decide as to how far the symptoms warrant a diagnosis of Haemophilia, for the members of the family may perhaps attach too much importance to the bleeding and tend to exaggerate the symptoms.

Under these circumstances no two observers are likely to come to the same conclusions on the question of inheritance, and, indeed, this difficulty must always be present whenever a differential diagnosis has to be made.

The most accurate results are undoubtedly obtained when a family is tainted with some obvious malformation, for members of the family are likely to take some interest in the hereditary transmission of their family defect.

In such a case personal examination of all the abnormals is hardly necessary, though desirable from the point of view of accuracy ; but in many families tainted with comparatively mild defects this examination is really

necessary before any value can be attached to the results.

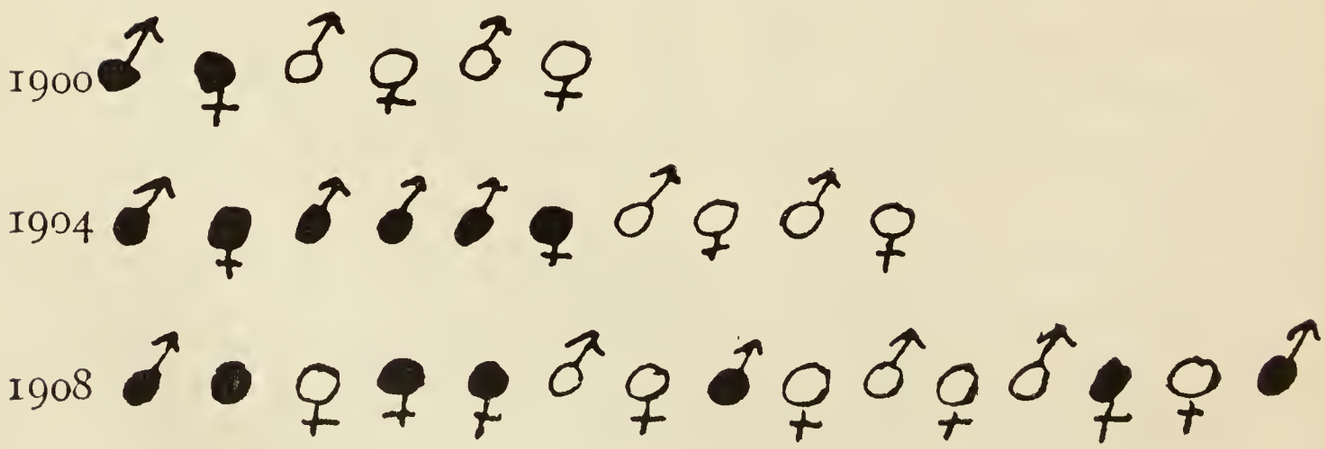
The tracing of a defect in the different branches of a family is a task which may or may not present difficulties, but the personal inspection of a large number of related individuals is often quite out of the question.

A transmission pedigree, however, is always useful, though it may be imperfect; it shows us more or less plainly the type of transmission prevalent in a family, and it helps us to understand the distribution of a defect in a childship.

For accurate information we must depend on the study of the childship which is under actual observation.

This contemporary childship is the expression of the limits of hereditary transmission, and the transmission pedigree serves its purpose for corroboration of the evidence obtained from a study of the childship.

It is necessary that every member of the childship should be accounted for whether alive or dead, and that in the case of obvious malformations miscarriages should not be overlooked. The importance of paying attention to such details is well illustrated by the following childship from a split hand and foot family which came under the notice of three different observers in the years 1900, 1904, and 1908.



The first record deals only with the living, the second with the living and the dead, while the third gives a complete childship of the living, dead, and miscarriages.

The fact that this childship can show so much variation, which is entirely dependent on the care of the observer, suggests that much revision of family histories is required for the correction of possible errors.

Revision of histories, too, has one great advantage, for new childships may have come into existence in the meanwhile, and these can be added to the pedigree.

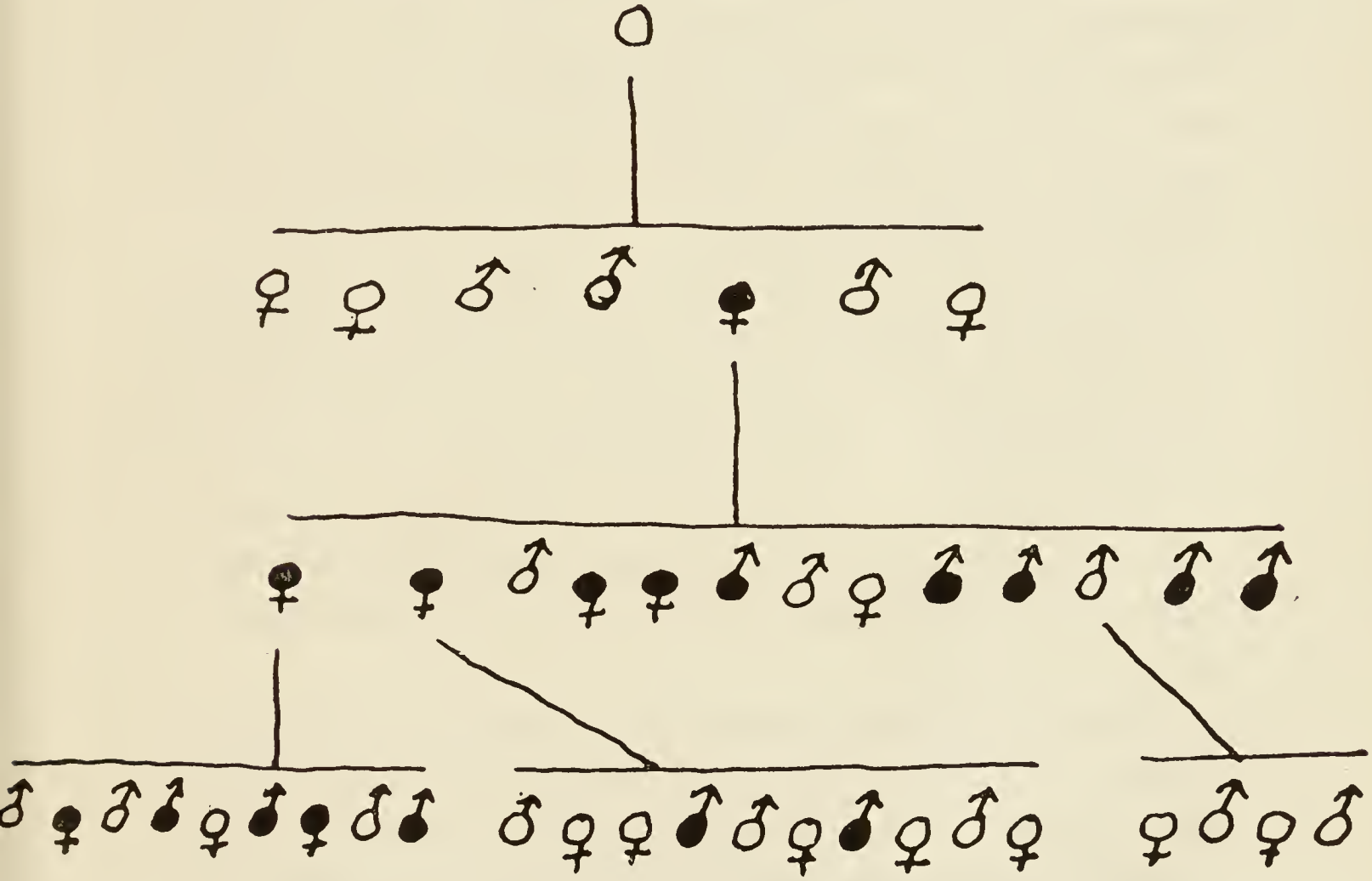


FIG. 33. MALFORMATION OF HANDS AND FEET.
Parker and Robinson, *Trans. Clin. Soc. London*, 1887, vol. xx, p. 181.

The family described by Parker and Robinson in 1887 (Fig. 33) may for this reason be compared with the same family described by Robinson and Bowen in 1909 (see

Fig. 2); it will be noticed that the addition of the new childships makes this pedigree a very important one for any statistical inquiry.

Having then suggested some of the difficulties which have to be faced when pedigrees are to be used for statistical purposes, we will attempt to bring forward evidence in favour of the principles of Mendelian inheritance.

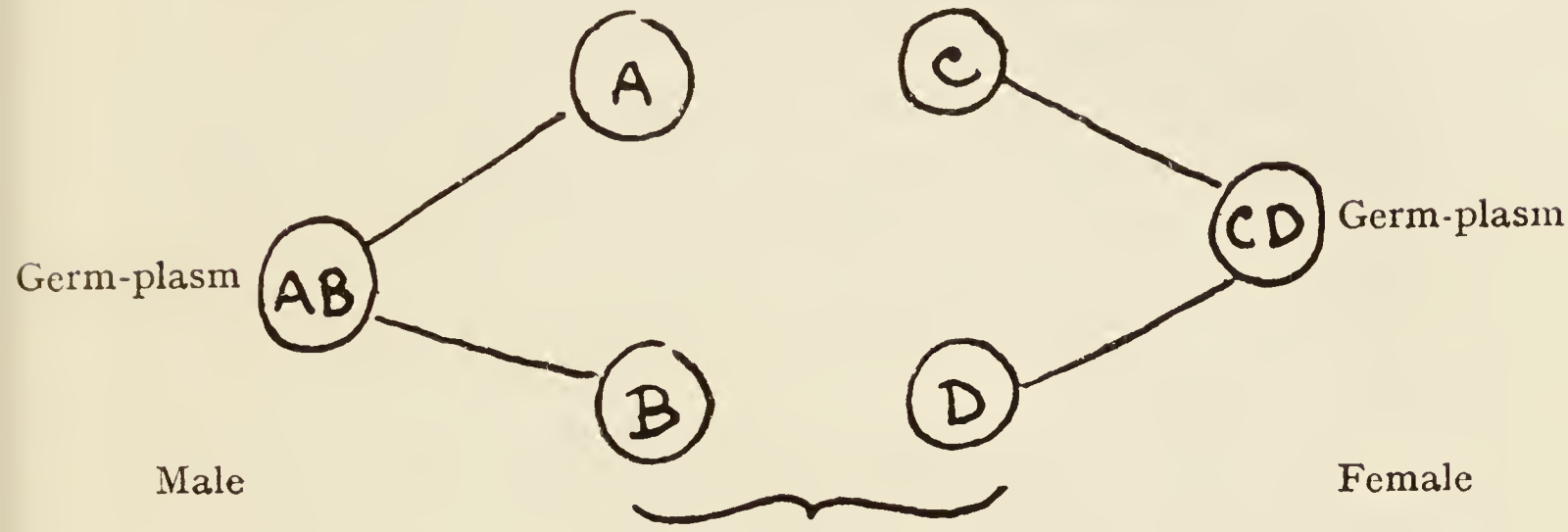
We have already shown that the type of transmission in families is a varying quantity, and for this reason it is necessary that the types of transmission should be considered separately if the exact proportion of abnormals and normals has to be determined. The extreme types of transmission are therefore more suitable for our purpose, for we know from examination of the pedigrees that the type of transmission is more or less fixed for the time being in any given family.

The relative proportion of abnormals and normals in a childship will depend on formulae based on the second postulate of Mendelian inheritance, namely, that the dual units segregate in the reproductive cells.

This segregation provides for the dissociation by means of cell division of the two units representing a somatic character, so that each unit is present in one-half of the reproductive cells.

If the dual units representing a character be AB in the male and CD in the female (Fig. 34), fertilization will bring about a new association of the units, and each fertilized ovum will contain one of the four possible pairs of units, namely AC, AD, BC, and BD. The somatic character of any given child will therefore be determined by the chance association of two units, one derived from each parent; and in the event of the character being defective, one or both of these determining units must be defective. In common direct transmission we are well

acquainted with a large number of families in which a defect is observed to be handed down directly from many individuals to their respective childships.



REPRODUCTIVE CELLS.
FIG. 34.

On the supposition that the germ-plasm of the abnormal parent carries a pair of dissimilar units, one *x* being defective, and the other *y* similar to those *yy* present in the germ-plasm of the other parent, the distribution of the units in the childship will depend on the formula

$$\begin{matrix} x & y \\ \times & \\ y & y \end{matrix} = xy.xy.yy.yy.$$

and half of the children will carry the defective unit *x* and therefore show a defective somatic character.

The simplest way of determining the proportion of abnormals and normals would be to take a large number of childships where we are satisfied that one of the parents displays a defect.

The size of the childship must, however, be taken into account, for in some of the earlier published pedigrees it seems clear that only the abnormal members of the childship have been accounted for in the family history.

It follows, therefore, that the larger the size of the childship the less the chance of error from this source.

And again, since we are also attempting to determine the relative proportion of abnormal males to normal males, and of abnormal females to normal females, we propose for statistical purposes to leave out of consideration all childships containing less than four children, and in doing this we tend to avoid complication from the further possibility that the consecutive appearance of two or more defective children may decide the parents to have no more children.

We selected 37 families showing common direct transmission of the following defects: Various malformations of the hands and feet, Muscular Atrophies, Cerebellar Ataxia, Huntingdon's Chorea, Epidermolysis Bullosa, Tylosis of hands and feet, Milroy's disease, and Polyuria.

There were in these families 103 childships of 4 or more children from the marriages of abnormals, and these childships gave a total of 739 children, or an average of 7·17 children for a childship. There were 402 males, of whom 193, or 48 per cent., were abnormal, and there were 337 females, of whom 176, or 52 per cent., were abnormal. The total number of abnormals, male and female, was 369, and the total number of normals, male and female, was 370.

The actual figures were, in the first calculation, drawn out in five groups, and even these show striking uniformity.

Childships.	*Males.*		*Females.*		*Total.*
	Abnormal.	*Normal.*	*Abnormal.*	*Normal.*	
17	36	35	27	27	125
20	40	42	38	40	160
24	38	47	37	32	154
21	40	41	45	37	163
21	39	44	29	25	137
103	193	209	176	161	739

There is one possible source of error in such statistics, namely, that childships showing an entire absence of defective members may not always have been included in the pedigrees. We can perhaps eliminate this possibility to a large extent by turning our attention to really large childships, say of ten or more members, for it is improbable that an abnormal having ten or more perfectly normal children would be absolutely ignored by any observer.

Abnormal males	64
Normal males	71
Abnormal females	52
Normal females	60
	247

There were 22 of these childships, accounting for 247 children, or an average of 11·22 children for a childship, and again the figures are suggestive of equal proportions of abnormals and normals.

There were 62 childships containing 4 or more males, giving a total number of 316 males, and the actual number of abnormal males was 151, which approximates closely the expected number 158.

There were 46 childships in which there were 4 or more females, and of the total number of 219 females, 111 were abnormal, as against the expected number of 109·5.

All our observations therefore favour the conclusion that in common direct transmission abnormals and normals appear in equal numbers both in the male and female sexes. Although these results are extremely satisfactory as far as Mendelian inheritance is concerned, they do not prove conclusively that particulate inheritance is necessarily dependent on the representation of somatic characters by dual units, for it is quite conceivable that representation of characters by single units could with

common direct transmission produce exactly the same results.

We will now consider the carrier female type of transmission, which next to common direct transmission ought to prove satisfactory for estimating the proportion of abnormals and normals.

Since the abnormal female does not exist in this type of transmission, we have only to turn our attention to the abnormal and normal males, and these on theoretical grounds should be in equal proportions.

There is, however, an important point which can easily be overlooked, namely, that a female can be a carrier and yet have a childship of perfectly normal children.

In a childship containing only two males, each male may be either abnormal, A, or normal, N, and the two males will be either AA, AN, NA, or NN.

The childship containing the two normal males NN could only be included in our calculations in the event of one or more of the sisters of these males being proved to be carriers, and this introduces an element of uncertainty.

It is more satisfactory, therefore, to take into account only those childships in which abnormal males are known to be present, provided that due allowance be made for the absence of the normal childships purposely ignored.

In the case of childships containing two males we therefore find abnormals in only three of the possible four childships, and in these there will be 4 abnormals and 2 normals, so that in a series of two-male childships the proportion of abnormals would be 66·6 for every 100 males.

For the same reason, with three males in a childship one completely normal childship in eight, and with four-male childships one in sixteen must be allowed for.

By calculation it will be found that for three-male

childships the proportion of observed abnormals will be 57·1 per cent., which for four-male childships becomes 53·3 per cent.

In order, therefore, to ascertain the true proportion of abnormals to normals, the childships should be taken in groups according to the actual number of males in each childship, but this is found to be impossible from lack of sufficient material.

By selecting childships containing four or more males from families tainted with Haemophilia, Pseudo-hypertrophic Paralysis, Colour-blindness, Leber's Optic Atrophy, and Ichthyosis, we found that the number of childships amounted to 42, with a total number of 235 males, and of these 128 or 54 per cent. were abnormal.

Among these childships there were 22 containing 6 or more males, with a total number of 155 males, and of these 77 or 49·6 per cent. were abnormal.

These results cannot be so convincing as those found in the case of common direct transmission.

The childships are only those produced by the marriage of carrier females, and the only legitimate conclusion to be drawn from the figures is that these carrier females usually transmit a defect to half of their sons.

The childship of the abnormal male, on the other hand, probably does not show such an equal proportion of abnormal and normal males, for there is evidence accumulating which tends to prove that there is often no direct transmission from the abnormal male to his sons.

The marriage of an abnormal to an abnormal, both having the same defect, is necessarily a rare event, and this is unfortunate, considering how important this marriage must be for testing the principles of Mendelian inheritance.

The proportions of abnormal and normal children would

depend on the following formulae, x being the defective, and y the normal unit.

I. $\begin{matrix} x - x \\ \times \\ y - y \end{matrix} = xx.\ xy.\ xy.\ yy$

If both parents carried dissimilar units.

II. $\begin{matrix} x - x \\ \times \\ x - y \end{matrix} = xx\ xx.\ xy.\ xy.$

If one parent carried similar and the other parent dissimilar units.

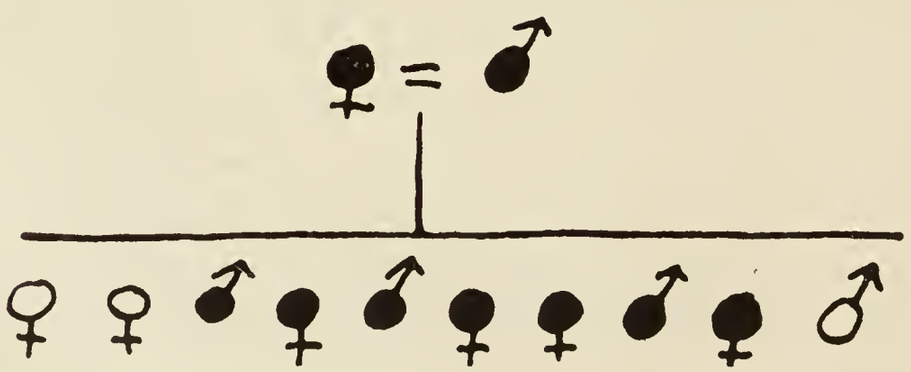
III. $\begin{matrix} x - x \\ \times \\ x - x \end{matrix} = xx.\ xx.\ xx.\ xx.$

If both parents carried similar defective units.

The first formula is the one most likely to be satisfied in the transmission of human defects, and this would demand in the absence of carriers that three out of four children should on the average be defective.

The following examples, although suggestive, are in point of number quite insufficient to warrant any definite conclusion as to the true proportion of abnormals and normals.

1



Senile Cataract.

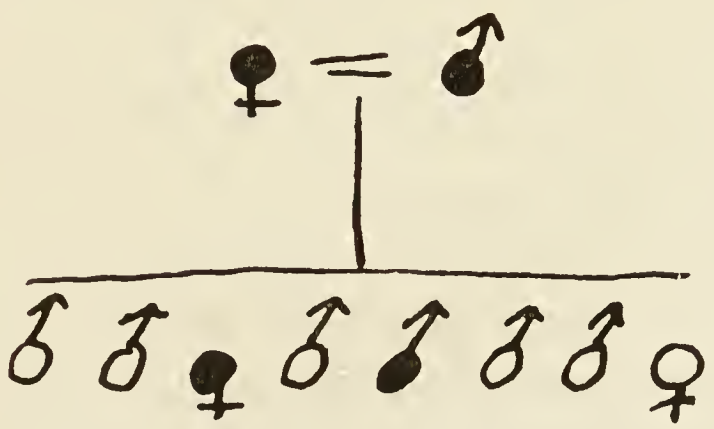
E. Nettleship, *Trans. Ophth. Soc.*, vol. xxviii, 1908, p. 220.

Parents. Female: Excellent sight till past 50. Operation for cataract at 72.
Male: Good sight till after 50. Operation for cataract at 85.

Children.
1. Eyes normal at 66.
2. Died at 45 with sight quite good.
3. Striae in lenses at 61.
4. Operation for cataract at about 54.
5. Two small striae in R. lens at 57. Became 'short sighted' at about 45.
6. Incomplete cataract known to be present at 48.
7. Operation for cataract at 53.
8. Marginal striae and small scattered opacities in both lenses at 48.
9. Rather more advanced changes than in No. 8 at 47.
10. Eyes normal at 45.

Conclusion. Omitting 2 and 10 as too young for the onset of the cataract, there were seven abnormals out of eight children.

2



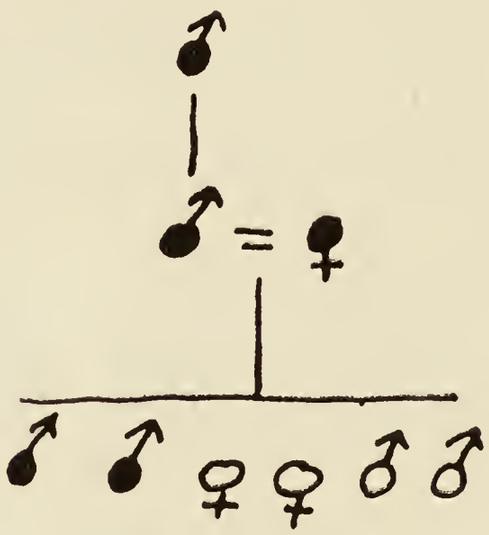
SENILE CATARACT.
E. Nettleship, *Trans. Ophth. Soc.*, vol. xxix, 1909, p. 188.

Parents. Female: Operation for cataract at 71.
Male: Became blind from cataract between 65 and 70.

Children. 1. Perfect sight at sixty.
2. Died in infancy.
3. Operation for cataract at 46.
4. Perfect sight at 54.
5. Striae in L. lens at 50.
6. Perfect sight at 47.
7. Died in infancy.
8. Died in infancy.

Conclusion. Omitting 2, 7, and 8, who died in infancy, there were at least two, with a possibility perhaps of there being eventually more than two, abnormals out of the five children.

3



Senile Cataract.

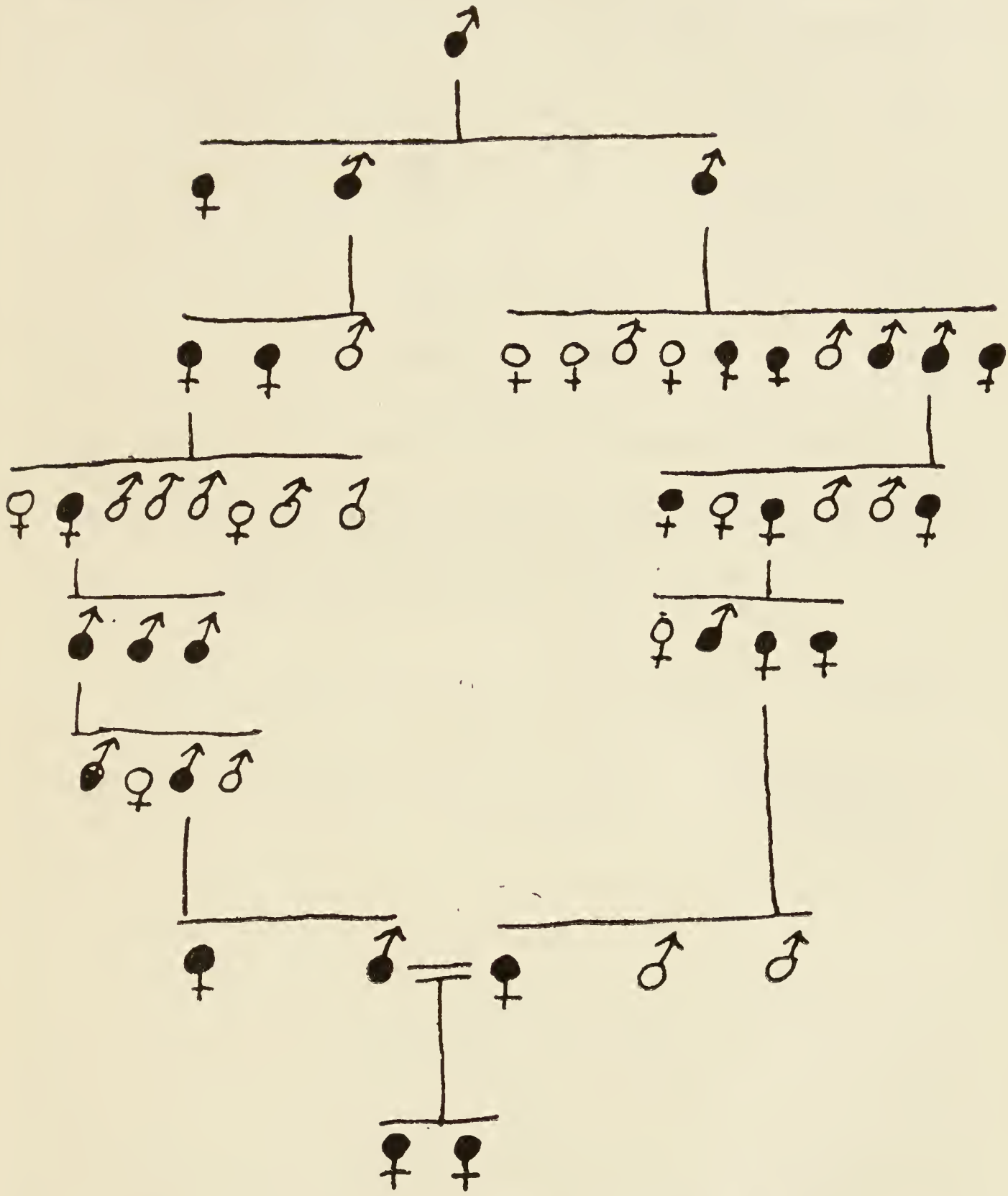
E. Nettleship, *Royal London Ophth. Hosp. Reports*, vol. xvi, Part III.

Parents. Female: Cataract.
Male: Cataract.

Children. 1. Cataract diagnosed at 57.
2. Operation for cataract.
3. Good eyes.
4. Good eyes.
5. Died of heart disease.
6. Drowned.

Conclusion. Omitting 4 and 6, there were possibly 2 abnormals out of 4 children.

4



CONGENITAL STATIONARY NIGHT-BLINDNESS.
E. Nettleship, *Trans. Ophth. Soc.*, vol. xxvii.

This pedigree deals with only two branches of Mr. Nettleship's famous Nougaret family, and it shows that the two parents were blood relations, besides being abnormal.

The two children from this marriage were both night-blind like their parents.

5

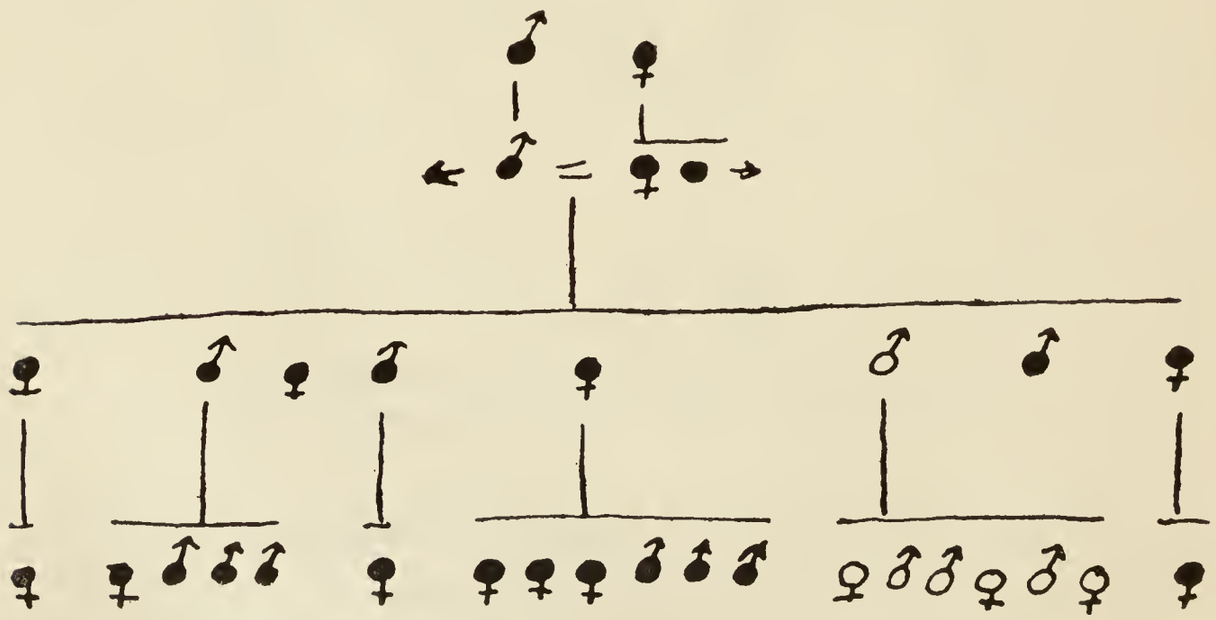
POLYDACTYLISM.
Drake Brockman, *Brit. Med. Journ.*, November 1892.

Parents. Male: Supernumerary little finger and toe on right hand and right foot.
Female: Supernumerary little finger on right hand.

Children. 1. Supernumerary thumb on right hand.
2. Supernumerary little toes on both feet.

It is possible here that the two abnormal children do not represent the whole childship.

6



WEBBED TOES.
H. P. Newsholme (unpublished).

A member of this family, the mother of the childship of six defective children, is at present a patient in St. Thomas's Hospital, and the facts of inheritance have been carefully investigated by Dr. Newsholme, House Physician.

The defect is a varying degree of webbing of the second and third toes of both feet, and this defect was present in all the members shown as defective in the pedigree with the exception of one male in the second childship of the last generation, who had webbing of the third and fourth digits of the right hand, the toes being normal. It will be noticed that in the second generation there was a marriage between a male and female, both of whom unquestionably had the same webbing of the toes.

In the childship from this marriage no less than seven out of eight children had the same defect.

We have, then, only six marriages to draw conclusions from, but considering that 22 out of 29 children in all probability showed the defect of their parents, the expected proportion of three abnormals to one normal certainly appears to hold good.

These marriages of two abnormals are important in one respect, in that they show that normal individuals can appear in the childship, and since the normal character is presumably represented in the germ-plasm of one or both parents, the principle of representation of somatic characters by dual units must be accepted as a necessity.

These marriages, again, are interesting from the fact that, according to the dual-unit hypothesis, they must produce individuals who carry two similar defective units, or in other words, individuals germ-saturated to a defect.

This germ-saturated individual on marriage with a normal would in the absence of carriers have a childship completely defective.

$$\begin{matrix} x & - & y \\ x & \times & y \end{matrix} = xy \cdot xy \cdot xy \cdot xy .$$

In Newsholme's family there are two childships in the youngest generation which are known to be completely defective, and which therefore may reasonably be considered to satisfy this formula.

The fact, however, that all the children in a childship are defective does not itself prove that the parent carries the two abnormal germ units, for by the laws of probability a childship may be totally defective even when the parent carries only one defective unit.

The expression $(1+1)^n$ gives the possible combinations of abnormals and normals for n children in a childship if there is an equal chance of each child being abnormal or normal, and one of these combinations represents a totally defective childship. A childship reputed to be totally defective must therefore be investigated with more than ordinary care, for we have to satisfy ourselves as to the reliability of the family history before calculating the probability of such an event occurring with common direct transmission.

As a matter of fact, large childships with all the children defective are of the greatest rarity, and they practically never come under the category of contemporary childships.

We have every reason to believe, therefore, that the germ-saturated abnormal plays quite an insignificant part in the transmission of human defects.

Having thus dealt with marriages in which one or both parents are defective, we will consider for a moment marriages in which both parents show no defect.

The appearance of a defect in the childship of these marriages may be explained on the assumption that one or both parents are carriers of the defect.

If one parent only is a carrier, the proportion of abnormals in the childship must be a varying quantity, but within certain limits.

With the female carrier type of transmission, for instance, one-half of the males are usually affected, so

FIG. 35. ALBINISM.
Childships from three families. (Private Notes.)

that on the average one-quarter of the childship would be expected to be abnormal. If, on the other hand, the carrier belongs to a family in which males and females act as both bearers and carriers, we should expect the proportion of abnormals in the childship to be under one-half and over one-quarter, and the average proportion to be somewhat over three abnormals in eight children.

The difficulties of using these marriages for statistical purposes become apparent when we consider each marriage on its own merits.

In three distinct families marriages of unrelated indi-

viduals produced childships in which albinoes appeared (Fig. 35), and at the same time there was in each case an absence of any history of inheritance to account for the presence of these albinoes. These childships could be brought forward to show the truth of the Mendel formula,

$$DR \times DR = DD,\ DR,\ DR,\ RR,$$

in which the recessive character, hidden in both parents, appears in one-quarter of the children.

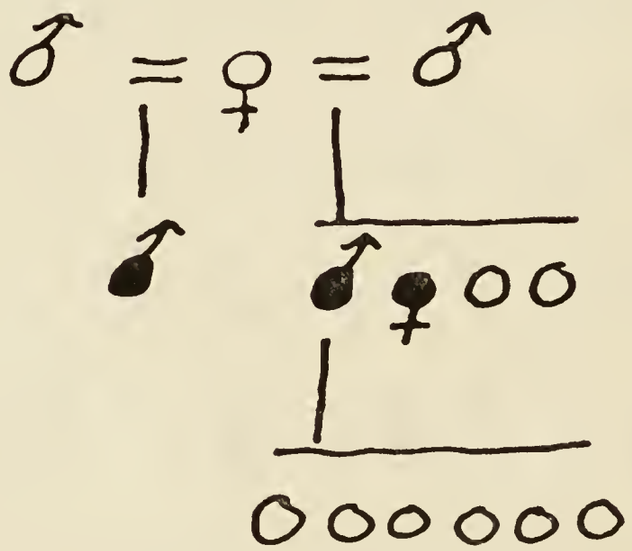


Fig. 36. Albinism.
Streatfield, *Lancet*, vol. i, 1882, p. 303.

On the other hand, the presence of albinism in these childships could equally well be explained on the assumption that only one of the respective parents was in each case a carrier of the defect.

If we take another family in which albinism appears (Fig. 36), it is highly improbable that the mother and her two husbands all carried the recessive character, whereas the fact that children from both husbands were albinoes points to the conclusion that the mother alone as a carrier was responsible for the appearance of the albino children.

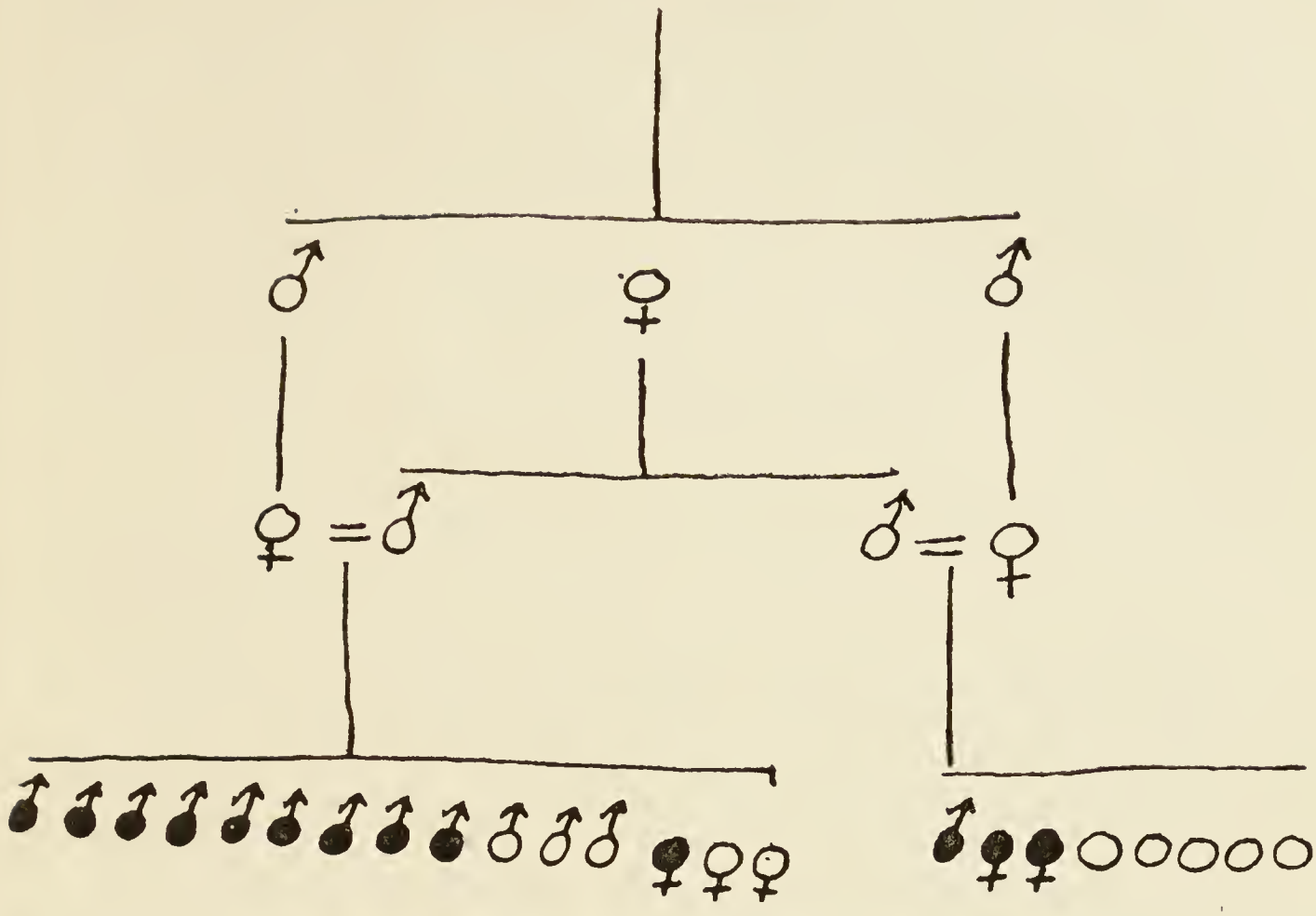


FIG. 37. ALBINISM.
G. O. S., October 1900.

D.W., an infant boy, one of a childship of fifteen, twelve males and three females, several of whom had died in infancy.

This infant had very light flaxen hair, very pronounced nystagmus, and almost complete absence of pigment in the eyes.

No less than ten out of the fifteen children had shown the same marked symptoms, and three cousins were similarly affected.

Albinism, again, can hardly be considered as a recessive character from its appearance in the large childship of fifteen children (Fig. 37), and we must conclude that the parents were both carriers as well as being first cousins.

If, however, this is a marriage of two carriers we must admit that there is much scope for speculation on the result of such a marriage.

$$\begin{matrix} x - x \\ \times \\ y - y \end{matrix} = xx.\ xy.\ xy.\ yy.$$

If this formula holds good for both males and females, one male in four and one female in four will certainly, as germ-saturated individuals, be albinoes, and for the same reason one male in four and one female in four will be normal.

Two males and two females will be carrying both abnormal and normal units in the germ-plasm, and therefore it is possible for all of them to become albinoes if the abnormal unit passes over into the somatic cells.

Now, indirect transmission teaches us that if the transmission comes through the mother, there is a tendency for half of the males to be abnormal and for half of the females to be carriers like their mother.

If, on the other hand, the transmission comes through the carrier father, there will be a tendency, but certainly not a marked tendency, for the females to be abnormal and the males to be carriers.

There are therefore two forces at work in the production of albinism in our childship.

Half of the sons, as sons of their carrier mother, should be abnormal, but as sons of their carrier father they could possibly be normal.

Half of the females, as daughters of their carrier father, may possibly be abnormal, but as daughters of their carrier mother they are more likely to be normal.

If the father and mother were to exert equal influence the result in a childship of eight children would be :—

One male and one female would be abnormal from germ-saturation, one abnormal male and one normal (carrier) female would show the influence of the mother, one normal (carrier) male and one abnormal female would show

the influence of the father, and one male and one female would be normal from germ-saturation.

Since the influence of the father on sex limitation is known to be much less than that of the mother, there is every possibility of the normal (carrier) male becoming an abnormal male. The childship would therefore become

and this, expanded into a childship of twelve males and four females,

suggests a ready explanation of the prevalence of albinism

childship.

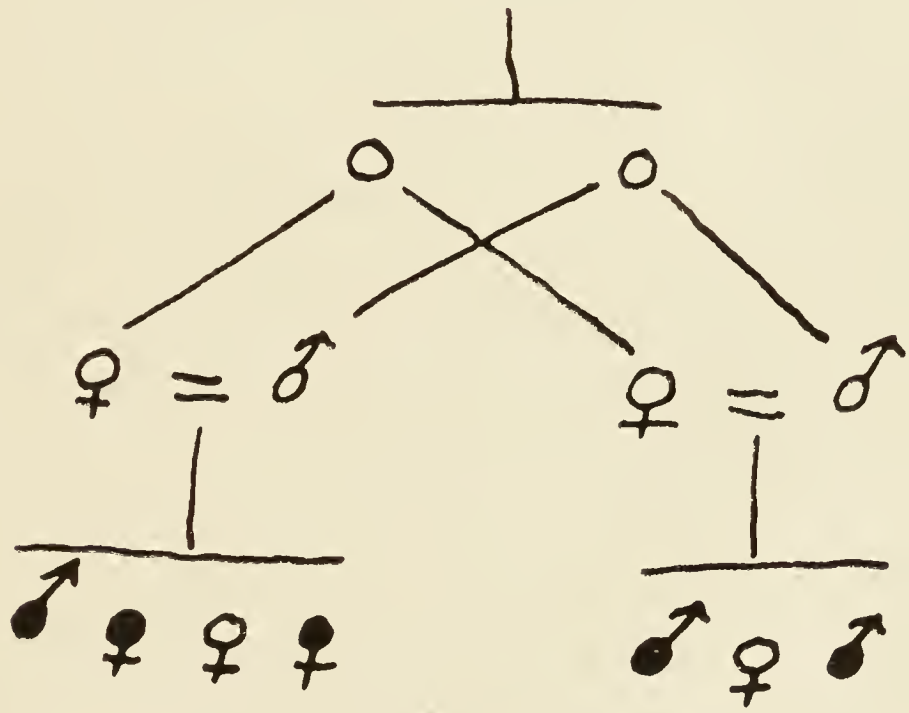


FIG. 38. RETINITIS PIGMENTOSA.
W. D. Lee's Family.
E. Nettleship, *Royal London Ophth. Hosp. Rep.*, vol. xvii, Part I.

A family tainted with Retinitis Pigmentosa (Fig. 38) also shows a large proportion of defective children as the result of two cousin marriages, but it must not be supposed

that the marriage of two carriers always produces such a large proportion of abnormals. It becomes a matter of great difficulty to decide whether one or both parents are carriers, and for this reason any attempt to prove Mendelian principles by applying statistical methods to such marriages is likely to be worthless.

To conclude, dual representation of somatic characters in the germ-plasm—the first principle of Mendelian inheritance—explains the behaviour of the carrier in transmission, and accounts for the appearance of normal children in the childship of abnormal parents. The facts of common direct transmission, and to a less extent of carrier female transmission, and the results seen with marriages of two abnormals, are perfectly consistent with a segregation and reassociation of these dual units.

The small size of human childships, the difficulty of avoiding questions of opinion on the diagnosis of certain defects, and the rarity of many defects, all help to check straightforward statistical inquiry.

The belief in hereditary transmission by dual units, nevertheless, is amply justified by experience gained in the cultivation of plants and in the breeding of animals, and for this reason is worthy of every consideration from the student of human inheritance.

OBSERVATIONS ON THE INHERITANCE OF I. ICHTHYOSIS, II. RED HAIR.

In bringing forward the following observations on the inheritance of Ichthyosis, it must be understood that the investigation which was commenced some years ago was not carried out with the idea of mere pedigree-making, but with the object of determining as far as possible the influence of heredity in a series of cases. Published pedigrees of hereditary transmission often deal only with the extreme possibilities, and therefore tend to give a wrong impression of the average possibilities of inheritance.

The patients were in the majority of cases seen in the Skin Department at St. Thomas's Hospital, and they were mostly children brought by one of the parents—usually the mother.

The first consideration was to determine the number of defective and normal children in the childship, and in many cases the other reputed defective members of the childship were brought to the hospital for inspection.

The next question was whether or not the rough condition of the skin had been or was present in either of the parents.

This question was seldom a source of difficulty, especially when the parent was informed of and realized the nature of the skin defect.

In all cases the father and mother were requested to ascertain if a similar defect had been known in their respective families, and considering that most patients

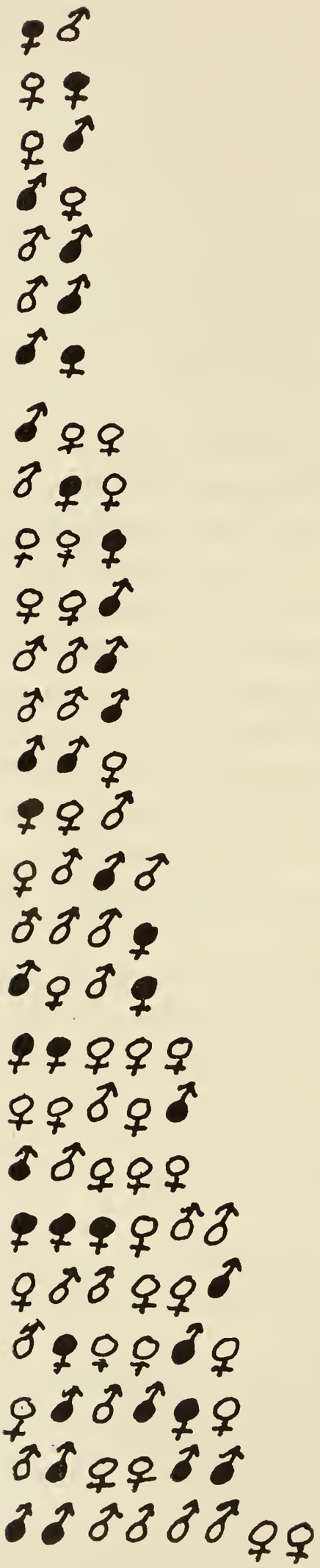


Fig. 39. Ichthyosis in twenty-seven Childships.
Parents and other relations reputed to be normal.

paid frequent visits to the hospital, there was every chance of obtaining some definite information on this point.

Some of the patients showed the disease in quite a mild form, and with these one could hardly expect to obtain much information of the disease beyond the childship and parents.

On the whole, when the disease was known to have been present in different generations of a family there was no difficulty in determining the exact numbers of defective and normal children. In such cases the members of the family seemed to be much interested in their inherited defect, and, moreover, were usually quite pleased to have a chat with the ' doctor ' on the subject.

There were forty-five families from which patients were observed, and in these families there were known to be 114 cases of Ichthyosis.

In twenty-seven of these families the Ichthyosis was limited to the childship under observation (Fig. 39), the disease being apparently absent in the parents and other relations.

It is somewhat surprising that a history of inheritance is wanting in such a large proportion of the families, but considering that we are dealing with hospital patients we cannot expect too much in this direction.

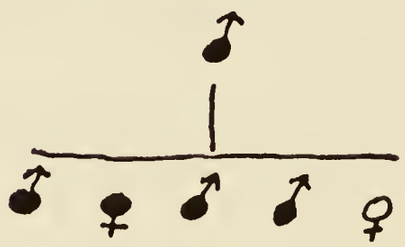
The important point is that the parents of these childships were as far as could be ascertained normal, so that presumably the defect had either come by indirect transmission through a carrier parent or had arisen spontaneously in the childship.

There were 103 children in these childships, and of these 39 or 38 per cent. had Ichthyosis.

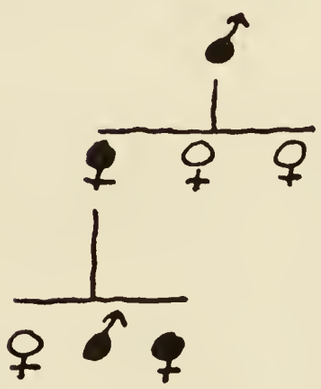
As a direct contrast to these families there were six families in which direct transmission occurred (Fig. 40), and it will be seen that of the twenty-eight children

M.D. 1907.

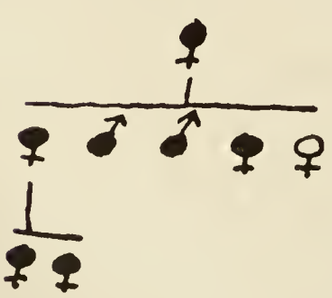
DR. 1903



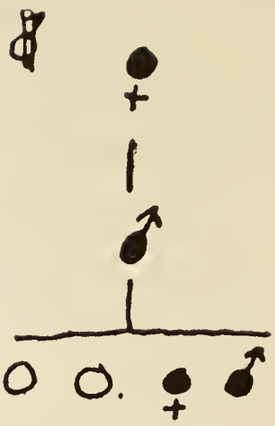
ER. 1907



D. 1908



A.W.P. 1900.



P. 1897.

FIG. 40. ICHTHYOSIS. COMMON DIRECT TRANSMISSION.

belonging to eight complete childships the large number of nineteen, or 68 per cent., had Ichthyosis.

If our twenty-seven childships without the history of inheritance are considered to be evidence for indirect transmission, the big drop from 68 per cent. of abnormals for direct transmission to 38 per cent. of abnormals for indirect transmission, is quite in keeping with our expectancy.

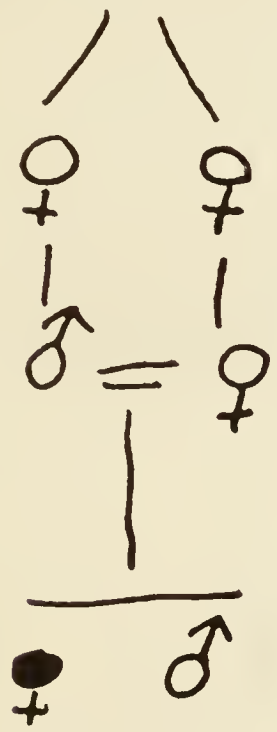


Fig. 41. N. S.

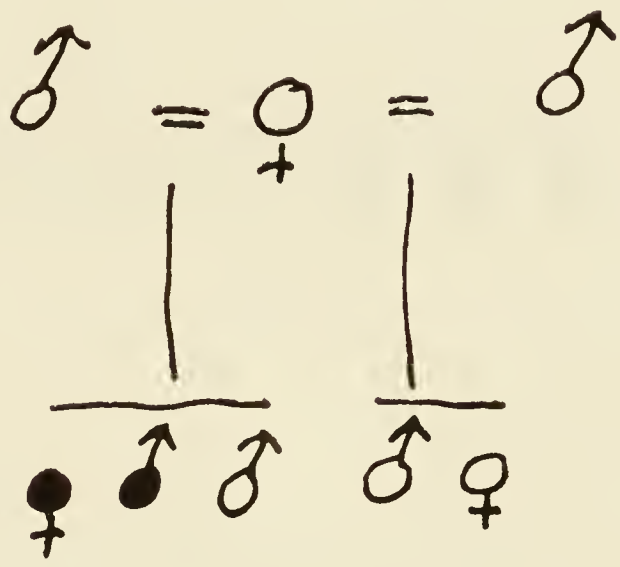


Fig. 42. G. L., 1905.

In one family (Fig. 41) the parents were first cousins, and in another family (Fig. 42) a female married twice and had two ichthyotic children by her first husband.

The remaining ten families show the various types of indirect transmission to be found in the disease.

The first (Fig. 43) shows both direct and indirect transmission.

The second (Fig. 44) suggests limitation of the defect to females with transmission through the male parent.

In the third (Fig. 45) the patient seen was the single defective member of the childship of nine.

The family history was supplied by the mother, and its correctness was verified by the testimony of another

relation who brought the patient to the hospital at a later date.

The fourth pedigree (Fig. 46) was obtained from a patient aged 18, who was being treated in one of the

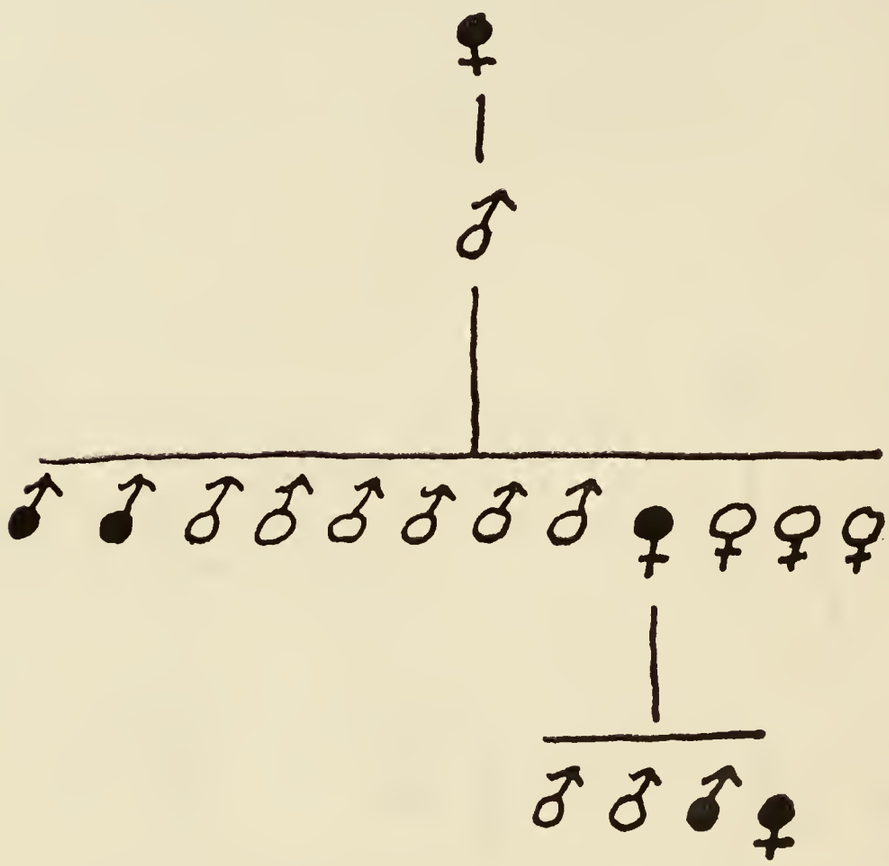


FIG. 43. T. F., 1902.

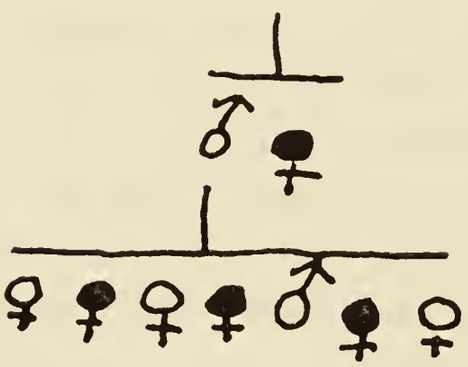


FIG. 44. L. B:, 1908.

wards for a nervous disease, and the information was supported by relations who were in evidence on visiting days.

The fifth pedigree (Fig. 47) is incomplete in that only the defective children are accounted for in the youngest generation.

In the sixth, seventh, and eighth families (Figs. 48–50) the mothers of the patients were certainly normal, and without hesitation stated that one of their parents had Ichthyosis.

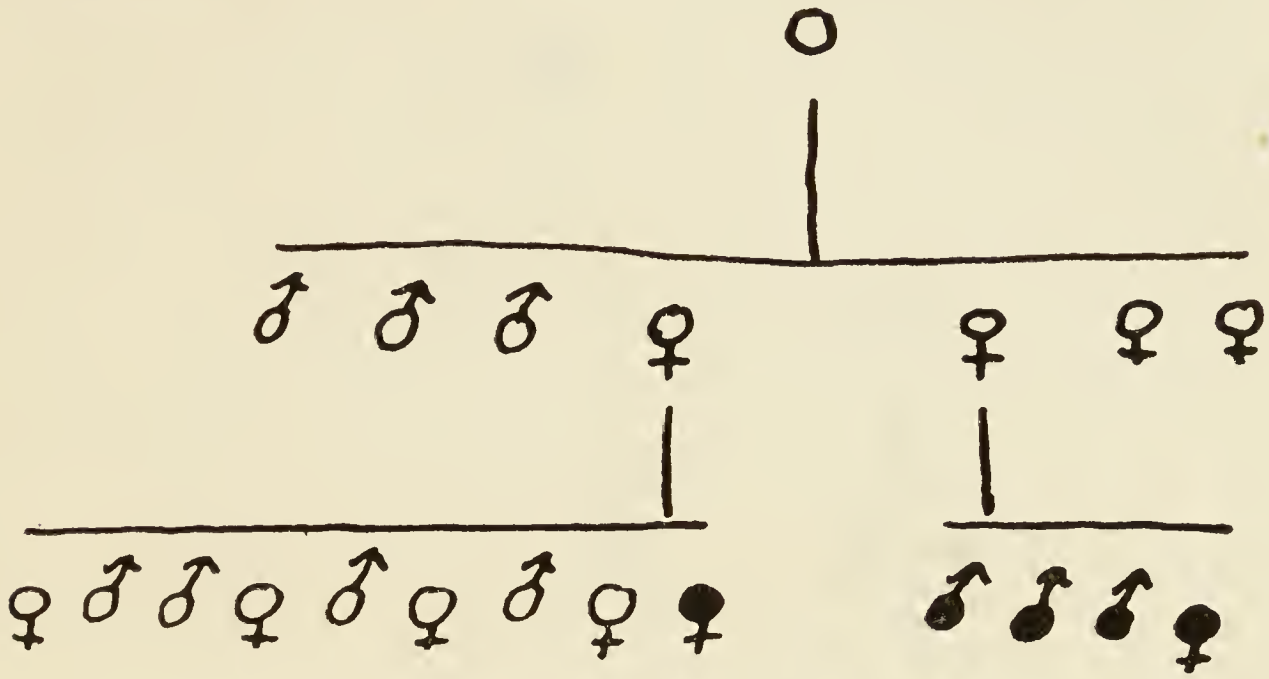


FIG. 45. M. E., 1900.

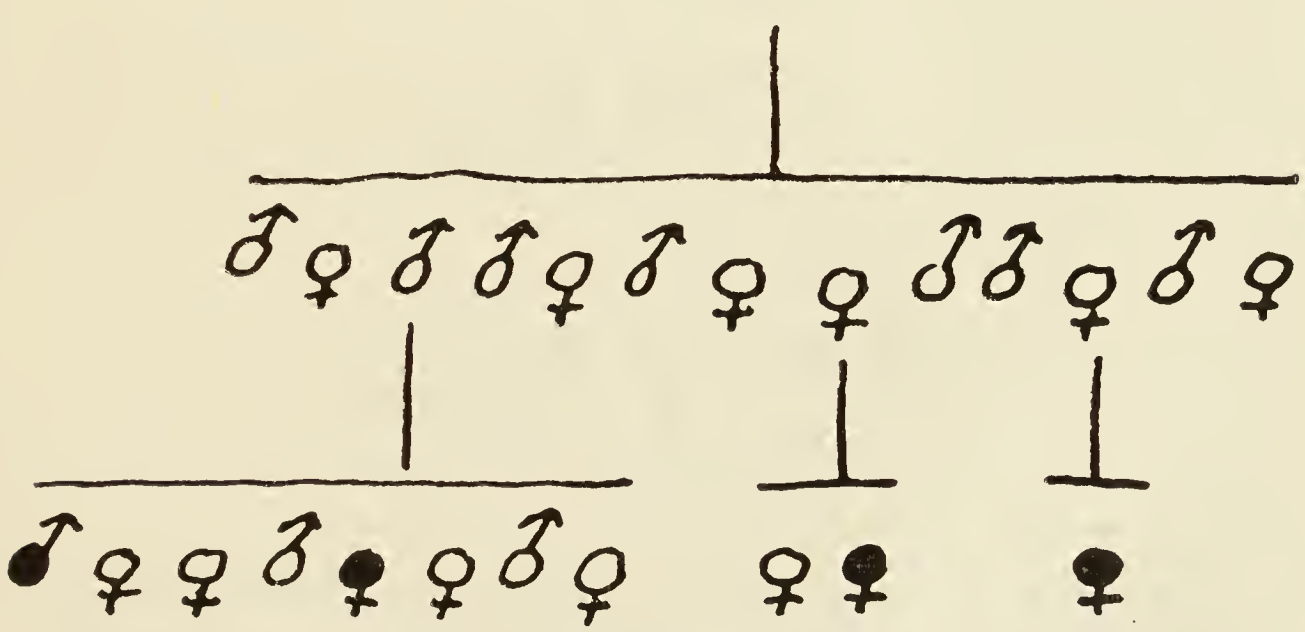


FIG. 46. W. W., 1899.

The ninth family (Fig. 51) shows the carrier female type of transmission.

The two males of the childship of four in the youngest generation were Dr. Colman's patients at the Hospital for Sick Children, Great Ormond Street.

The younger patient was 4 months old when examined, and showed the signs of early and well-marked Ichthyosis, which first became evident to the mother when the infant was only 6 days old.

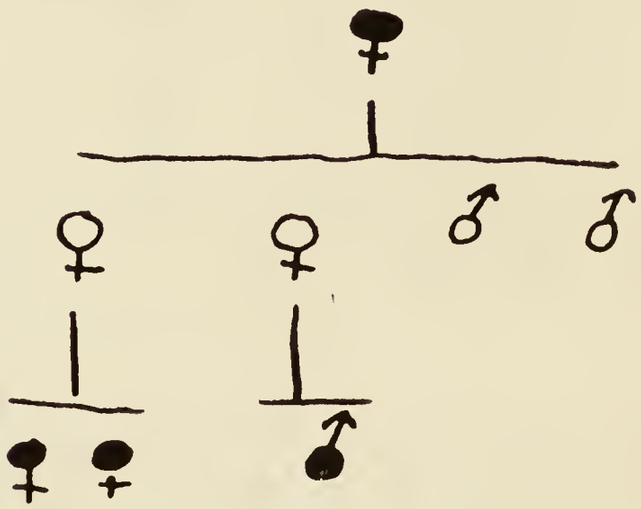


Fig. 47. F. O., 1900.

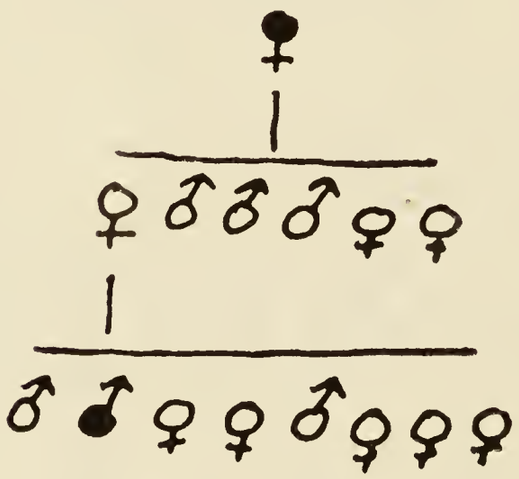


Fig. 48. B., 1899.

The elder brother, aged 6, had very rough and dirty-looking skin, and he too had shown the first signs of Ichthyosis when a few days old.

It will be noticed that there are no normal males in the pedigree, and this may be an error of omission. The youngest generation, however, may be considered as represented correctly.

The tenth and last family (Fig. 52) has already been

noticed (p. 16) for its carrier female type of transmission.

The pedigree was supplied by the mother, who stated that it was a well-known peculiarity in her family that if Ichthyosis made its appearance in a childship, it would be found in one boy only. The member of the family examined at the hospital was a boy who had the disease in a severe form, so much so that the defective dirty rough skin was strikingly evident on the hands, head, and neck. In the childships in which Ichthyosis appeared there were, omitting the first generation, twenty-three normal females and twenty males, of whom six had Ichthyosis.

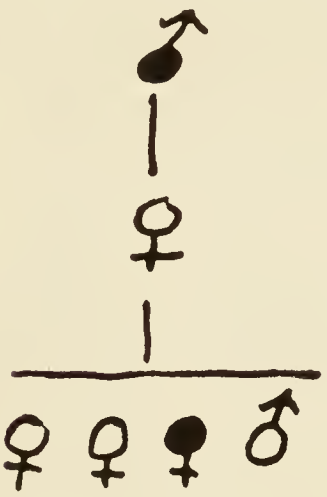


FIG. 49. L. C., 1900.

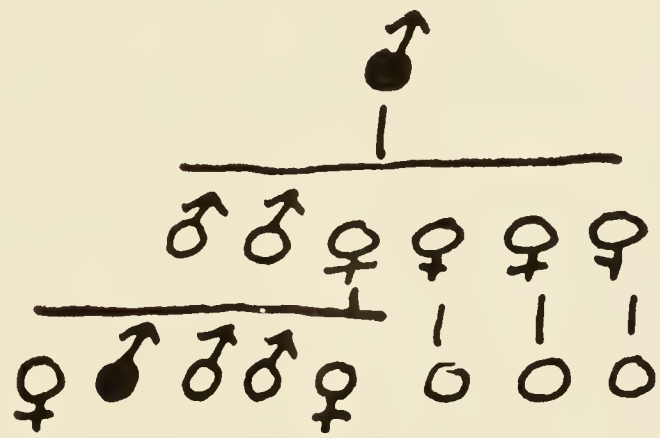


FIG. 50. W. H., 1901.

The small proportion of affected males to normal males in each generation suggests that there is an unequal segregation of normal and abnormal units, and, moreover, that this unequal segregation is a more or less fixed quantity for this family.

The degree of segregation as a family peculiarity is a question which requires more close attention, since it probably has much to do with the proportion of affected males not only in this but in the preceding family, in which normal males appear to be absent. We may conclude from this series of families that Ichthyosis can be transmitted in a variety of ways.

There is evidence of common direct transmission, of irregular indirect transmission, and of carrier female transmission. Ichthyosis in fact behaves like many other defects in being transmitted in all the possible ways indicated in our general scheme of transmission.

All defects, however, do not show the same amount of variation in transmission, and this is due in the first place to a comparative absence of carriers who are the immediate cause of this variation. Deformities of the

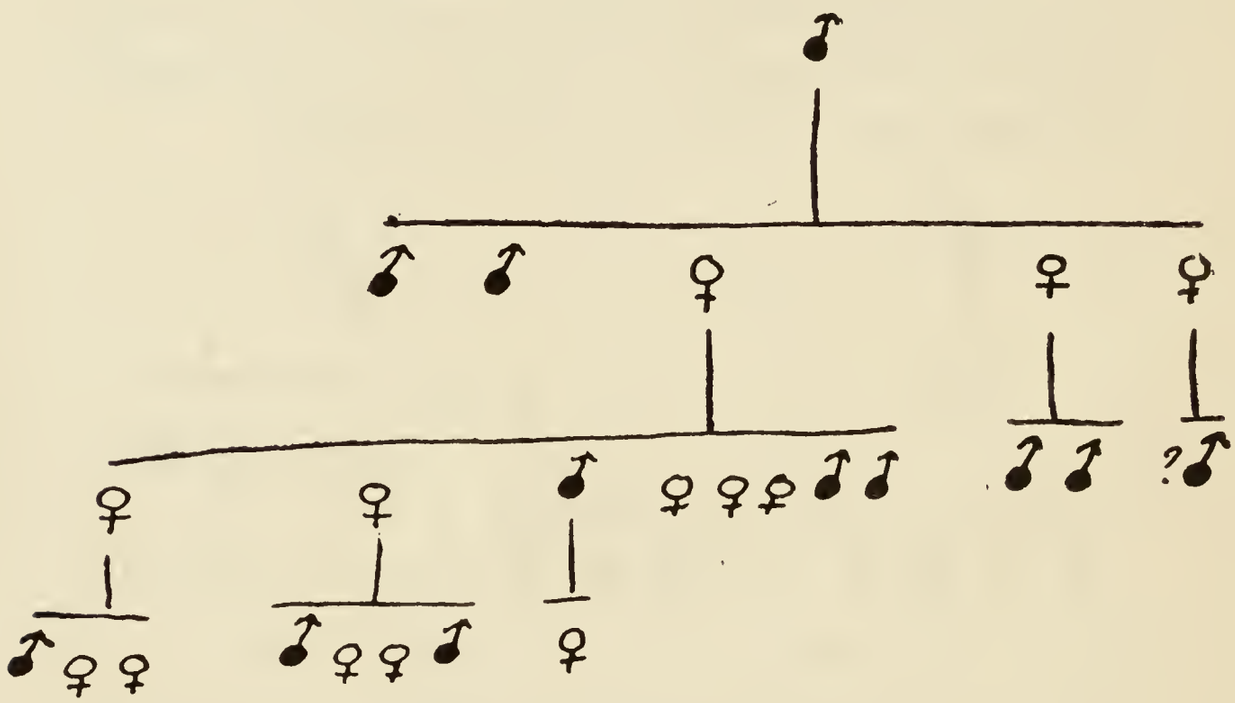


FIG. 51. G. D., 1900.

hands and feet are, for instance, usually transmitted directly from parents to children, and in many families the carrier is an unknown quantity.

No reasonable explanation can at present be offered for the behaviour of individual defects in this respect, for the quality of the defect does not appear to determine the type of transmission, although its influence is felt when marriage is checked.

If we turn from abnormal to normal characters we find much the same differences between one character and another.

Eye colour is known to be commonly transmitted from parents to children, and is then generally handed down by common direct transmission.

Hair colour, on the contrary, is certainly often transmitted indirectly, and for this reason should be more closely studied.

The hair often changes its colour during life, generally in the direction of darkness, and allowance must be made

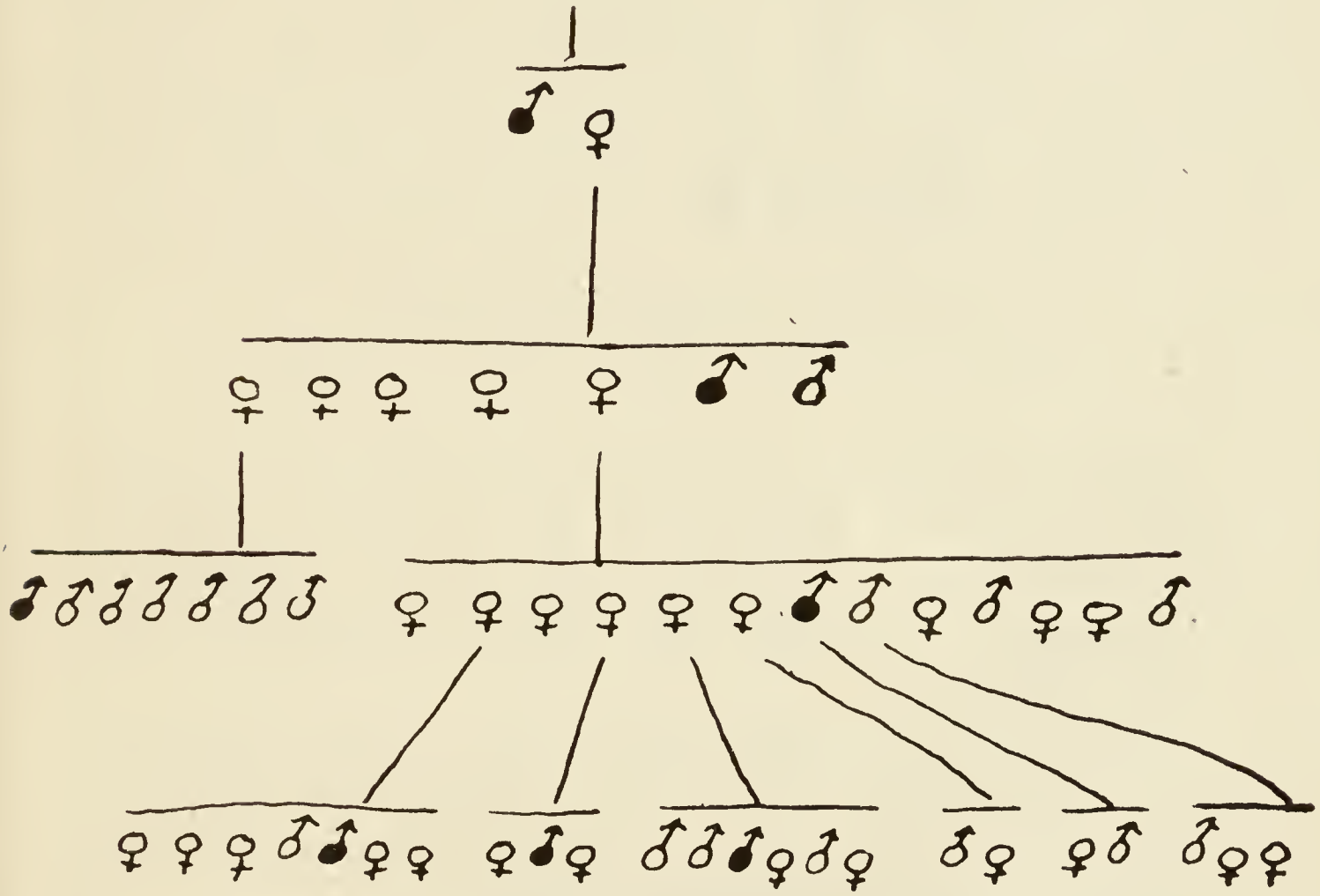


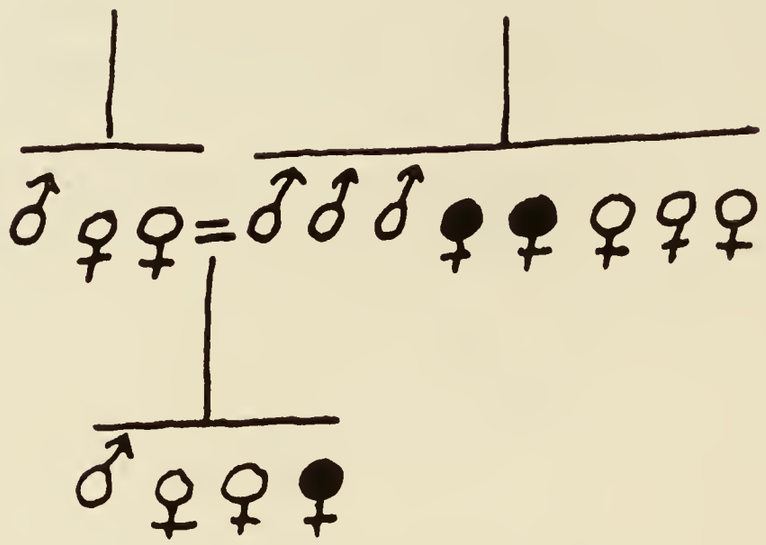
FIG. 52. H. B., 1897.

for such changes. A marked contrast in the hair colour of different members of a childship should always suggest the influence of hereditary transmission, as in the following case.

A fair-haired girl visited the hospital in company with her dark-haired brother, and the difference of colouring between the two was so striking that the facts of transmission were inquired into.

The mother supplied the following transmission pedigree,

in which three females were quite fair and all the rest of the individuals quite dark.



Fair Hair in Dark Hair Family.
J. H., St. Thomas's Hospital, January 1909.

The transmission in this family is clearly of the male carrier type with limitation of the character to females, and as such can be compared with similar transmission occurring in Ichthyosis and Muscular Dystrophy (see Figs. 26 and 27).

Red hair, of the bright variety, the ' carrots ' of school life, is often seen in one or more members of a childship, and the red-haired child is a marked contrast to its more sombre-coloured brothers and sisters.

A visit to a children's out-patient department at a hospital, or a stroll through one of our public parks, would be quite sufficient to convince any one of the truth of this fact. Inquiry as to the hereditary transmission of this hair often leads to the discovery of other red-headed individuals scattered here and there in the family, and, moreover, the transmission frequently comes indirectly through one of the parents.

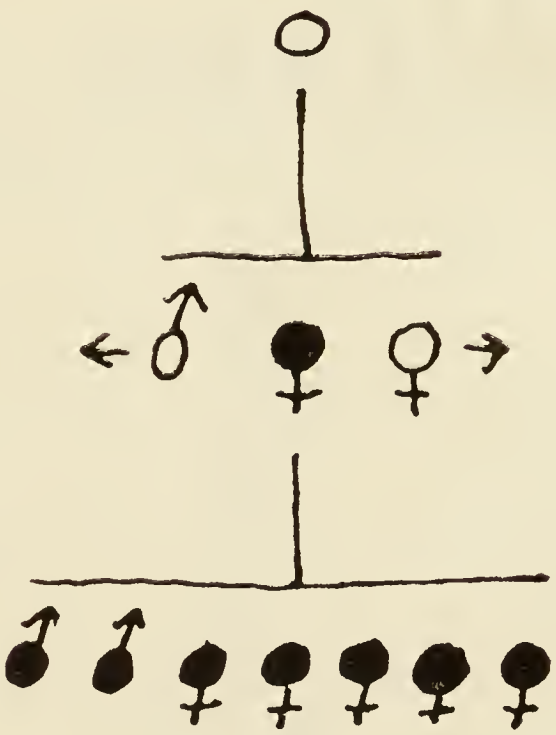
Red hair may exist in childhood, and then change in

colour during life either to a lighter colour or to a dark shade, with loss of practically all red colour.

In some cases confusion might arise from this change of colour, but in many cases the red hair seems to remain as a permanent adult character.

In bringing forward the following families, it must be remembered that the pedigrees are based on rough notes taken in a busy out-patient department, so that they in no way suggest an exhaustive inquiry into the colour tints of all the related individuals. The pedigrees merely deal with ' red ' and ' not red ' individuals, and in all cases the distinction between the two classes was sufficiently marked to justify the record of the family history.

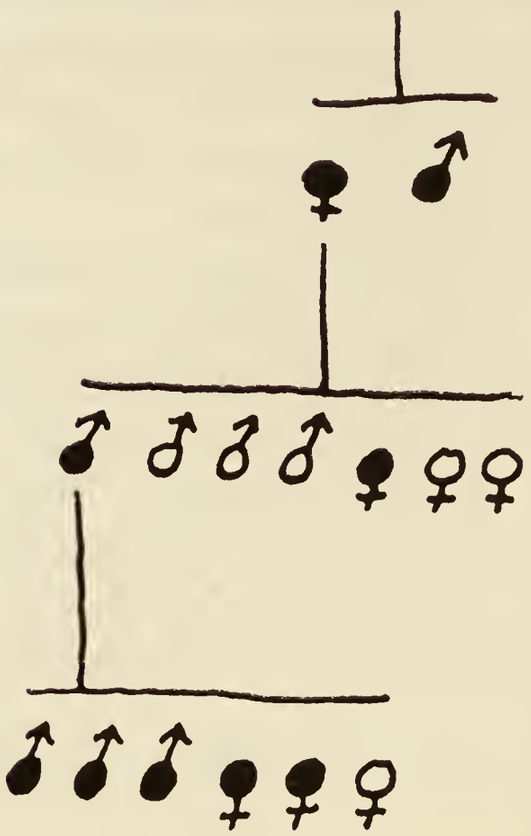
I.



The mother's hair was of a darker brownish red, but it had been bright red in childhood: her brothers and sisters showed no red tints, and her parents were both fair.

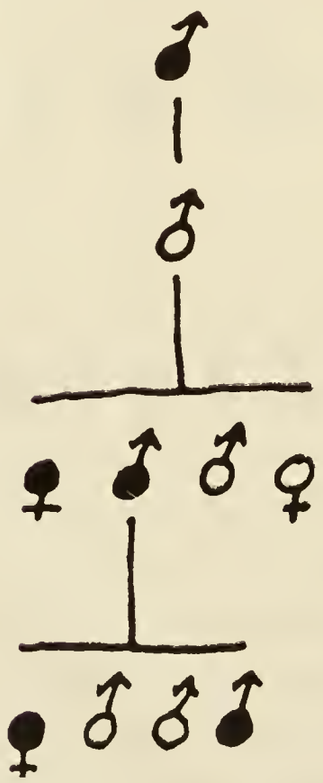
This childship may be explained in two ways: first, that the mother was germ-saturated to red hair, so that all the children carried the unit; second, that the childship was the result of common direct transmission, this being possible in a seven-child childship once in 128 cases.

II.



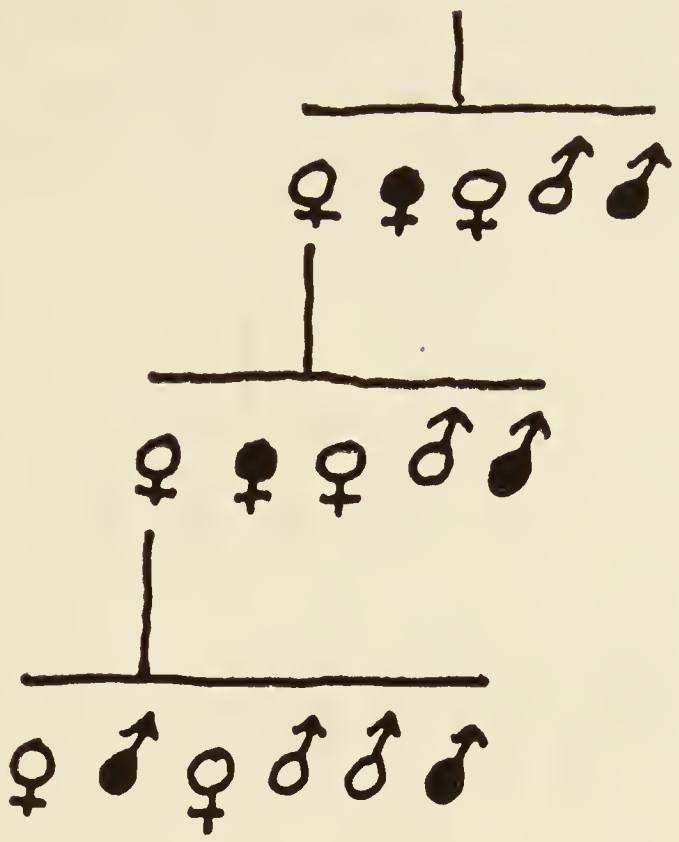
This family shows ordinary direct transmission.

III.



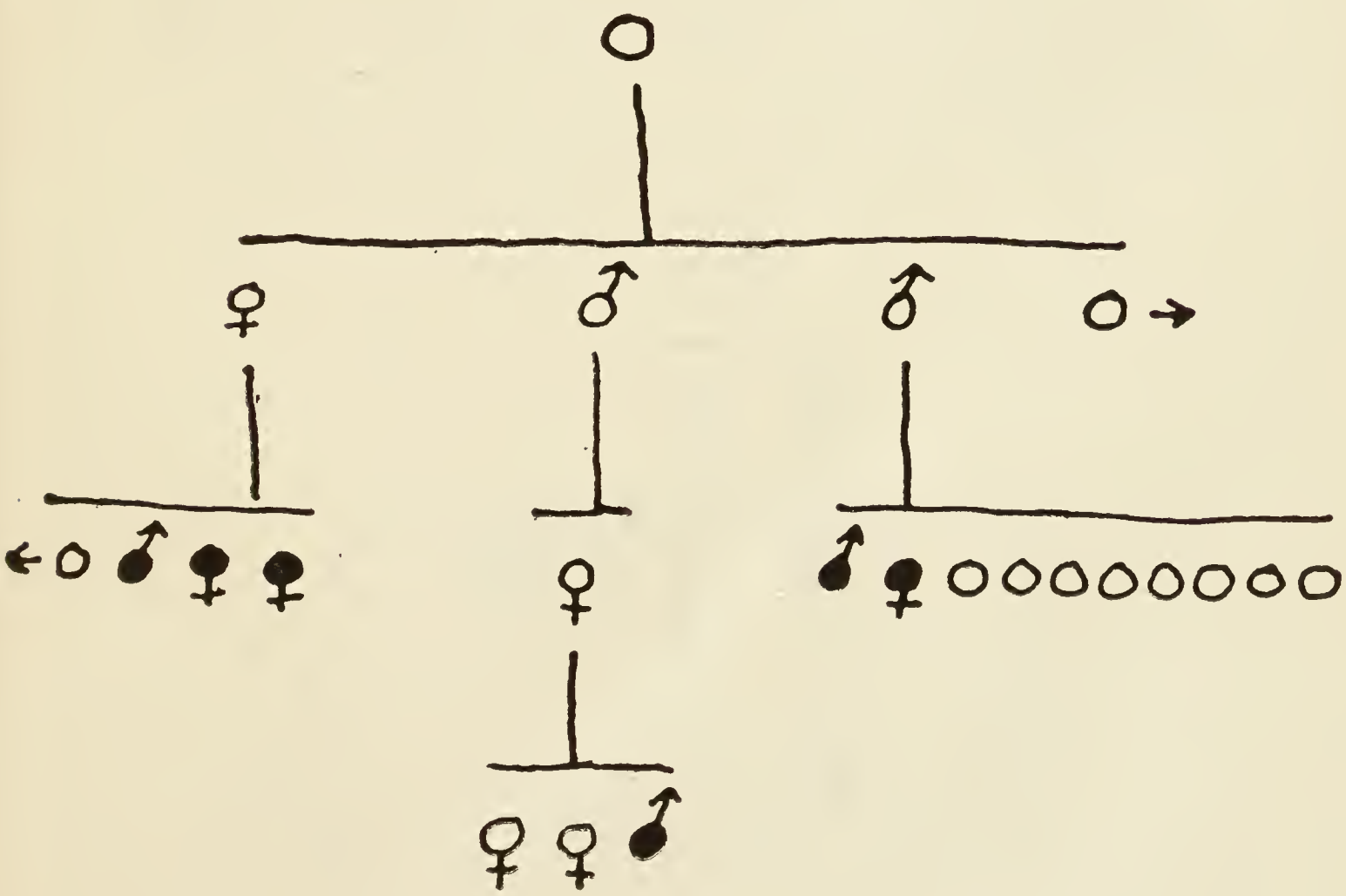
Here we have direct and indirect transmission both occurring.

IV.



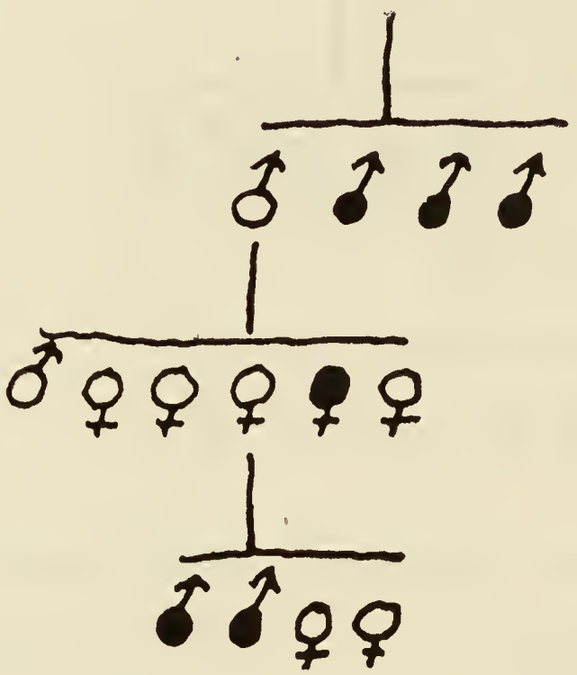
Here is indirect transmission in one branch of a family, through females but without definite limitation of the character to males.

V.



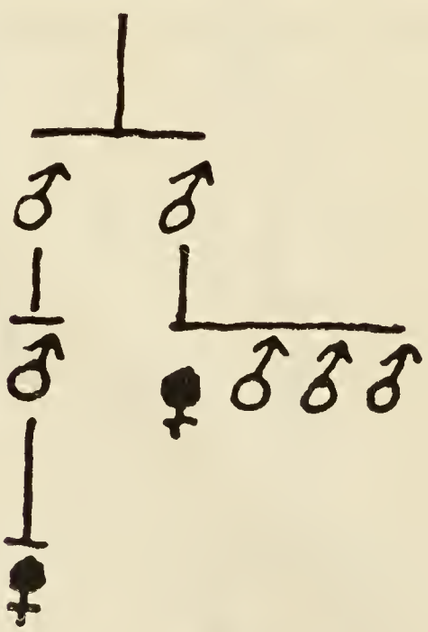
This shows indirect transmission in three branches of a family through both males and females, but without any suggestion of sex limitation to the red hair.

VI.

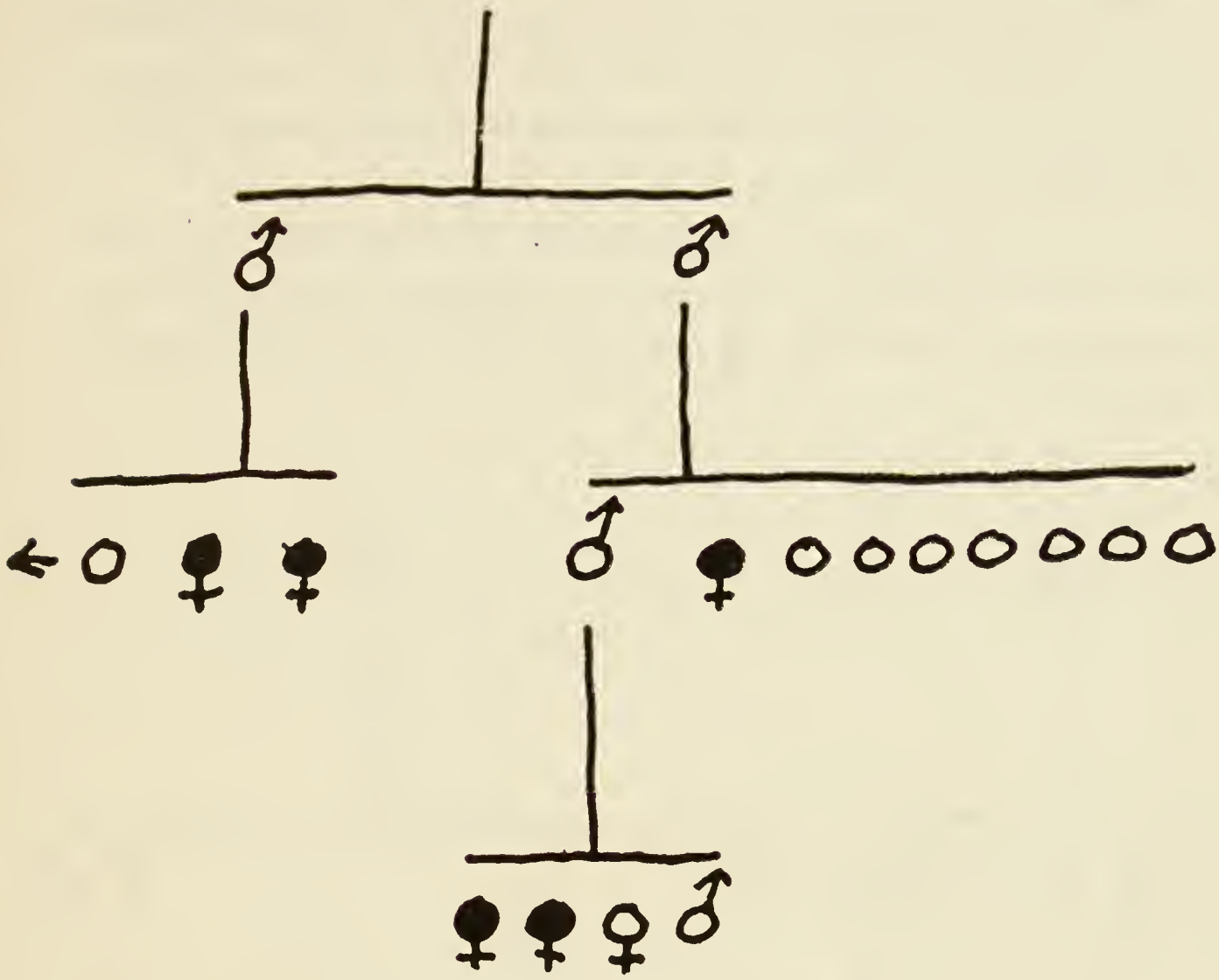


Here there is a suggestion of sex limitation, the red hair coming to a female through her father and to two males through their mother.

VII.



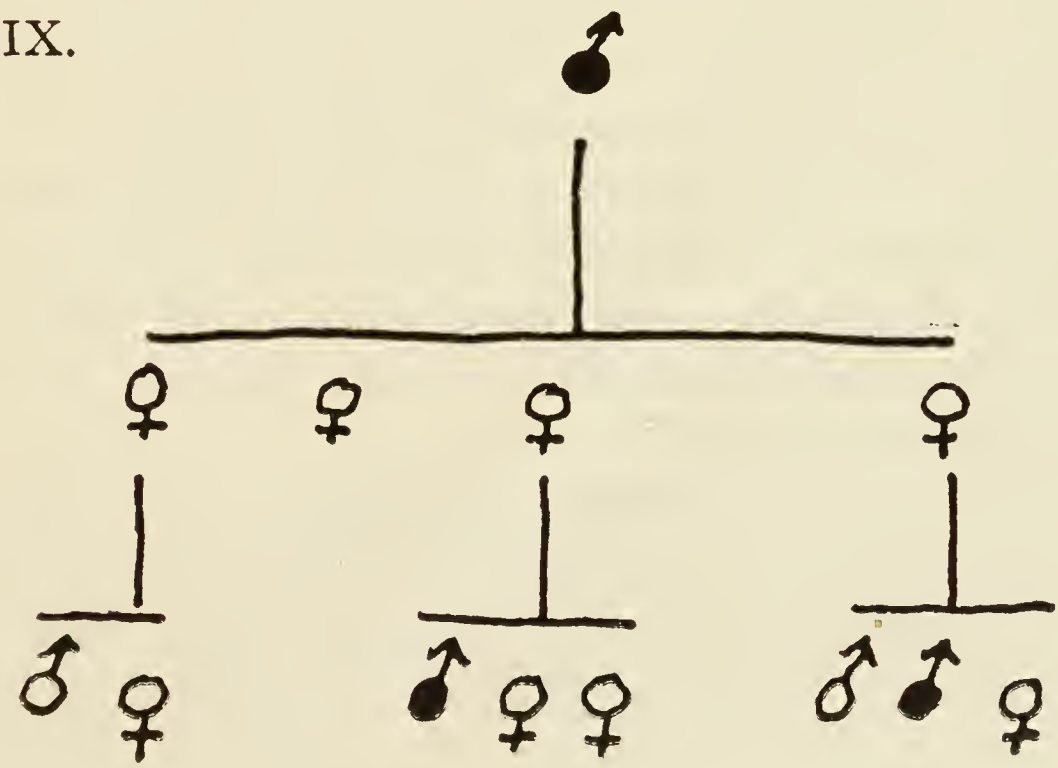
VIII.



These two families show the red hair only in females, and the transmission is in every case through the fathers.

They both may therefore be looked upon as examples of the male carrier type of transmission.

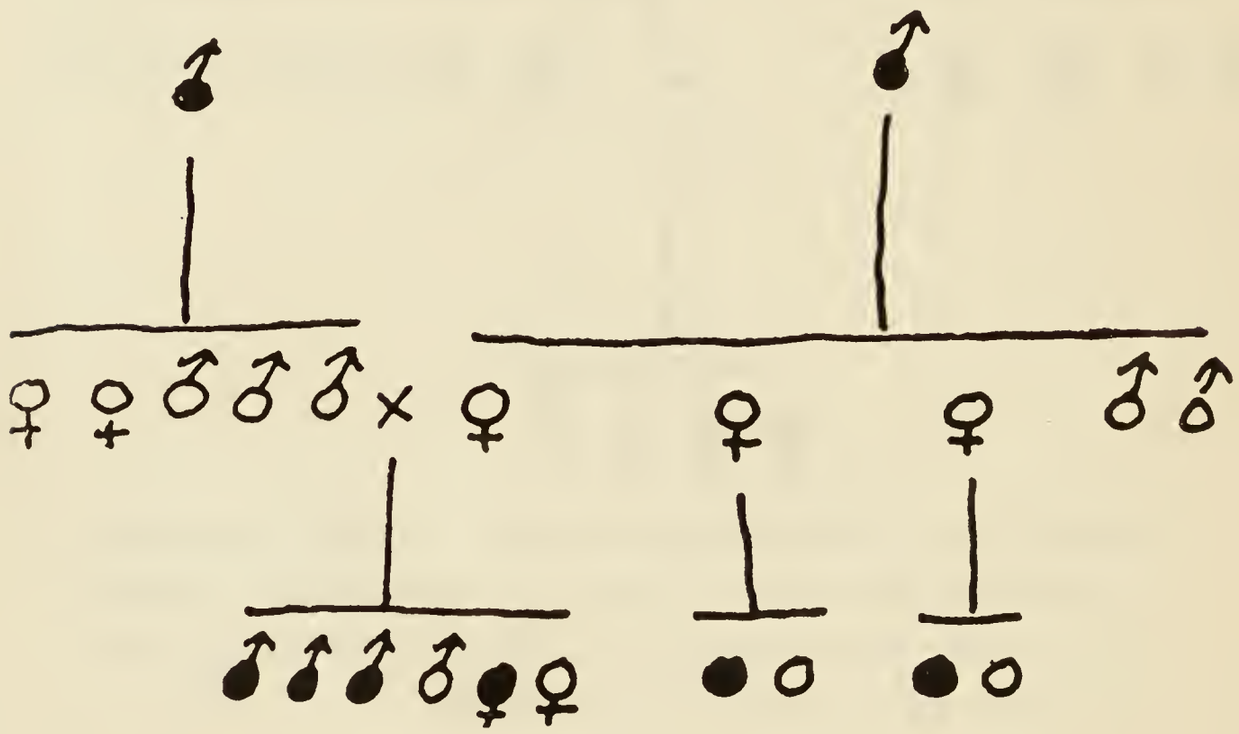
IX.



Here, in contrast to the two preceding families, we have an example of the carrier female type of transmission, in which the males only have red hair with transmission through their mothers.

It is interesting to note too, in this family, that one of the red-headed boys in the youngest generation was considered to be the very image of his red-headed grandfather.

X.



This pedigree is again interesting from the fact that with indirect transmission four out of six children are red-headed. It will be noticed that the maternal and paternal grandfathers are both red-headed, and it is therefore possible that both parents are carriers, in which case the preponderance of red hair in the childship is easily explained (see p. 74).

This selection of families suggests, therefore, that red hair is transmitted in much the same manner as Ichthyosis. The relative frequency of carriers no doubt makes this possible, and indeed must always influence the type of

transmission in the case of any character, whether abnormal or normal.

Common direct transmission, for instance, is the type of transmission associated with characters which are usually handed down by bearers.

Characters usually transmitted by both bearers and carriers are, on the other hand, passed down by common direct transmission, irregular indirect transmission, and carrier female transmission. Lastly, characters which are usually transmitted by carriers, or which, from their rendering marriage impossible, can only be transmitted by carriers, are almost invariably handed down in families by carrier female transmission.